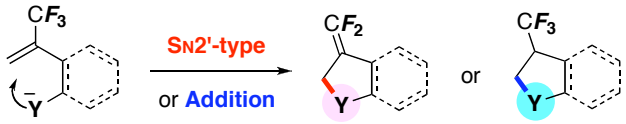
A New Class of Substrates for Nucleophilic 5-endo-trig Cyclization, 2-Trifluoromethyl-1-alkenes: Synthesis of Five-Membered Hetero- and Carbocycles That Bear Fluorinated One-Carbon Units

doi: 10.1002/asia.200700324

5-*endo-trig* Cyclization

Junji Ichikawa, Yu Iwai, Ryo Nadano, Takashi Mori, Masahiro Ikeda*

A New Class of Substrates for Nucleophilic 5-*endo-trig* Cyclization, 2-Trifluoromethyl-1-alkenes: Synthesis of Five-Membered Hetero- and Carbocycles Bearing Fluorinated One-Carbon Units



Y = **N**Ts, **O**, **S**, **C**(EWG)$_2$

Disfavored ring formation: 5-*endo-trig* Cyclizations are achieved in 2-trifluoromethyl-1-alkenes with a nucleophilic nitrogen, oxygen, sulfur, or carbon atom via (i) intramolecular S$_N$2′ reaction with loss of a fluoride ion or (ii) intramolecular nucleophilic addition to the vinylic group.

DOI: 10.1002/asia.200((……))

A New Class of Substrates for Nucleophilic 5-*endo-trig* Cyclization, 2-Trifluoromethyl-1-alkenes: Synthesis of Five-Membered Hetero- and Carbocycles Bearing Fluorinated One-Carbon Units

***Junji Ichikawa,*[a] *Yu Iwai,*[b] *Ryo Nadano,*[b] *Takashi Mori,*[b] and *Masahiro Ikeda*[a]**

The present work is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

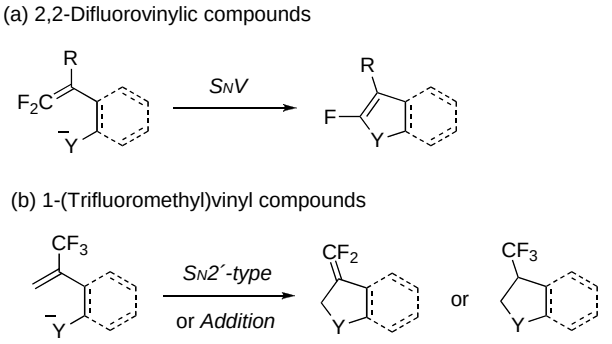
Abstract: Disfavored 5-*endo-trig* cyclizations are achieved in 2-trifluoromethyl-1-alkenes with a nucleophilic nitrogen, oxygen, sulfur, or carbon atom via (i) intramolecular S_N2' reaction with loss of a fluoride ion or (ii) intramolecular nucleophilic addition to the vinylic group. This reaction manifold provides a versatile method for the synthesis of indolines, indoles, pyrrolidines, tetrahydrofurans, 2,3-dihydrobenzo[*b*]thiophenes, tetrahydrothiophenes, and cyclopentanes bearing a fluorinated one-carbon unit such as a difluoromethylene, difluoromethyl, or trifluoromethyl group.

Keywords: 5-*endo-trig* cyclization, fluorine, heterocycles, carbocycles, synthetic methods

Introduction

The 5-*endo-trig* cyclization has long been considered to be a geometrically disfavored process according to Baldwin's rules.[1] Reported examples of this disfavored ring closure are classified into three categories: nucleophile-driven,[2,3] electrophile-driven,[4] and radical-initiated cyclizations.[5] Among these, nucleophile-driven 5-*endo-trig* cyclizations have rarely been observed in synthetic chemistry, compared with the two other types of cyclization.

In our recent studies, we have accomplished the normally disfavored nucleophilic 5-*endo-trig* cyclizations with 1,1-difluoro-1-alkene substrates (2,2-difluorovinylic compounds) bearing a functional group such as NHTs, OH, SH, or CH_2I (Scheme 1a).[2] Deprotonation or lithium–iodine exchange of these groups generates *N*-, *O*-, *S*-, and *C*-nucleophiles, which successfully undergo a vinylic addition–elimination (S_NV) process to construct five-membered ring-fluorinated heterocycles and carbocycles such as indoles, 2-pyrrolines, benzo[*b*]furans, 2,3-dihydrofurans, benzo[*b*]thiophenes, 2,3-dihydrothiophenes, and cyclopentenes. Such unique reactivities of 1,1-difluoro-1-alkenes are presumably the result of (i) the highly polarized C=C double bond, which allows the initial five-membered ring formation by electrostatic attraction of the positive CF_2 carbon for the nucleophiles, and (ii) the subsequent elimination of fluoride ion, which suppresses the reverse ring opening.



Scheme 1. Nucleophilic 5-*endo-trig* Cyclization of Fluoroalkenes.

Among fluoroalkenes, 2-trifluoromethyl-1-alkenes are also known to possess an interesting reactivity in nucleophilic reaction, resulting from (i) the highly electrophilic double bond with a strong electron-withdrawing CF_3 group and (ii) the good leaving group ability of allylic fluorine atoms. The nucleophilic reaction of 2-trifluoromethyl-1-alkene substrates [1-(trifluoromethyl)vinyl compounds] proceeds with the accompanying elimination of an allylic fluorine (S_N2'-type process), which provides a potential method for the preparation of 1,1-difluoro-1-alkenes.[6] We have recently conducted the S_N2'-type reaction with nitrogen and carbon

[a] Prof. Junji Ichikawa, Masahiro Ikeda
Department of Chemistry
Graduate School of Pure and Applied Sciences
University of Tsukuba
Tsukuba, Ibaraki 305-8571 (Japan)
Fax: (+81)29-853-4237
E-mail: junji@chem.tsukuba.ac.jp

[b] Yu Iwai, Dr. Ryo Nadano, Dr. Takashi Mori
Department of Chemistry
Graduate School of Science
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

Supporting information for this article is available on the WWW under

nucleophiles in an intramolecular fashion to construct six-membered rings. Furthermore, we have observed them to undergo addition and substitution in the presence and absence of a proton source, respectively. These reactions readily provided quinoline and isoquinoline derivatives bearing a CF_3, CHF_2, or $=CF_2$ group under mild reaction conditions.[7]

Such a high reactivity of that 1-(trifluoromethyl)vinyl moiety prompted us to examine the geometrically disfavored 5-*endo-trig* cyclization, which might allow the development of a new synthetic route to five-membered ring systems bearing fluorinated one-carbon units (Scheme 1b). Indeed, the presence of nucleophilic centers on the position β to the 1-(trifluoromethyl)vinyl group might lead to either an intramolecular S_N2'-type process or an addition reaction, depending on the conditions, and thus deliver five-membered cycles.

Five-membered heterocycles and carbocycles constitute important classes of compounds in pharmaceuticals, agrochemicals, materials, and catalysts. In these fields of science, the introduction of a fluorine atom or fluorocarbon substituents has come into wide use as one of the most efficient methods for modification of biological activity as well as of physical and chemical properties.[8] Among fluorocarbon substituents, fluorinated one-carbon units (CF_3, CHF_2, $=CF_2$, and CH_2F) are quite attractive:[9] (i) the incorporation of a trifluoromethyl (CF_3) group into organic molecules increases lipophilicity and affects electron density,[10] (ii) a difluoromethyl (CHF_2) group has hydrogen bond donor ability without nucleophilicity and with high lipophilicity,[11] which makes it a special mimic of a hydroxy group,[12] and (iii) a difluoromethylene ($=CF_2$) group acts as a reactive site towards nucleophiles[13] and a potential isostere of carbonyl groups,[14] and provides a CHF_2 group via its reduction.[15] Nevertheless, synthetic methods for heterocycles and carbocycles with these fluorinated one-carbon units are limited and remain to be developed.

The preliminary results of the 5-*endo-trig* cyclizations of 1-(trifluoromethyl)vinyl compounds have been briefly reported in our previous communication, where we focused on those with intramolecular nitrogen nucleophiles.[16] Combining the results of those obtained with other nucleophiles such as oxygen, sulfur, and carbon resulted in this full account of our studies on the 5-*endo-trig* cyclizations of 1-(trifluoromethyl)vinyl compounds, yielding difluoromethylene-, difluoromethyl-, and trifluoromethyl-substituted indoline, indole, pyrrolidine, tetrahydrofuran, benzo[*b*]thiophene, tetrahydrothiophene, and cyclopentane derivatives.

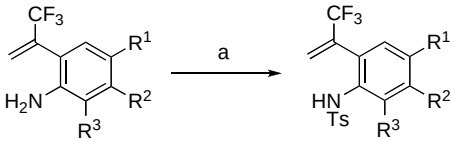
Results and Discussion

Preparation of the Cyclization Precursors

Abstract in Japanese:

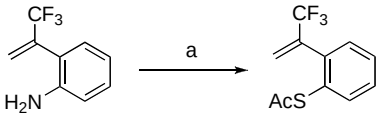
分子内に窒素、酸素、硫黄、炭素求核種を有する 2-トリフルオロメチル-1-アルケンにおいて、これまで困難とされてきた求核的 5-*endo-trig* 環化を達成した。この 5 員環形成反応は、（i）フッ化物イオンの脱離を伴う分子内 S_N2'反応、もしくは（ii）ビニル基への分子内求核付加を経て進行する。これら一連の反応により、ジフルオロメチレン基、ジフルオロメチル基、トリフルオロメチル基のような含フッ素 1 炭素ユニットを有するインドリン、インドール、ピロリジン、テトラヒドロフラン、2,3-ジヒドロベンゾ[*b*]チオフェン、テトラヒドロチオフェン、およびシクロペンタンを合成することができる。

We first selected α-(trifluoromethyl)styrenes bearing a nucleophilic nitrogen or sulfur at the *o*-position as 2-trifluoromethyl-1-alkene substrates for 5-*endo-trig* cyclization, because of the previously reported favorable effect of a 1-aryl group in 1-(trifluoromethyl)vinyl compounds undergoing S_N2' reaction.[6b] 2-(3,3,3-Trifluoroprop-1-en-2-yl)-substituted anilines **1** were prepared by the palladium-catalyzed coupling reaction of *o*-iodoaniline with (3,3,3-trifluoroprop-1-en-2-yl)boronic acid, obtained from the magnesium-mediated Barbier-type reaction of 2-bromo-3,3,3-trifluoropropene with trimethyl borate, following a literature procedure.[7a,17] Sulfonylation of the amino group of **1** gave anilides **2** (Scheme 2). Introduction of an *S*-functionality was effected via diazotization of the amino group. Treatment of **1a** with *i*-AmONO and CF_3CO_2H, followed by the addition of sodium thioacetate, gave thiophenol ester **3** (Scheme 3).



1a: R^1 = H, R^2 = H, R^3 = H — **2a** 84%
1b: R^1 = Me, R^2 = H, R^3 = H — **2b** 87%
1c: R^1 = H, R^2 = Cl, R^3 = H — **2c** 92%

Scheme 2. Preparation of 2´-(3,3,3-Trifluoroprop-1-en-2-yl) Sulfonanilides **2**. *Reagents and conditions*: (a) TsCl (1.2 equiv), DMAP (0.1 equiv), 0 °C to rt, 12 h, pyridine.



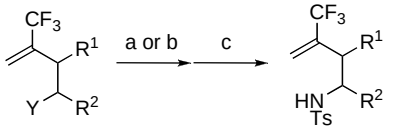
1a — **3** 31%

Scheme 3. Preparation of *o*-(3,3,3-Trifluoroprop-1-en-2-yl) Thiophenol Ester **3**. *Reagents and conditions*: (a) TFA (2.0 equiv), *i*-AmONO (2.0 equiv), 0 °C, 0.5 h, MeCN.

In addition, we designed nonconjugated substrates lacking a phenylene tether, 3-(trifluoromethyl)homoallyl sulfonamides, alcohols, thiols, and malonic acid derivatives, as second-type precursors of hetero- and carbocycles. Two methods were employed for the construction of these skeletons: (i) addition of 2-trifluoromethyl-substituted allylsilane to aldehydes[18] and (ii) ring opening of oxiranes with 1-trifluoromethyl-substituted vinyllithium,[19] prepared by treatment of 2-bromo-3,3,3-trifluoropropene with *n*-BuLi, both of which provided 3-(trifluoromethyl)homoallyl alcohols **4**. The Mitsunobu reaction of **4** with BocNHTs,[20] followed by deprotection of the Boc group afforded the cyclization precursors **5** (Scheme 4). 3-(Trifluoromethyl)homoallyl alcohol **4a** was also adopted as a cyclization precursor feachering a nucleophilic oxygen. α-Alkylated ketones **6**, prepared from **4** via oxidation and alkylation, were reduced to give homoallyl alcohols **7** bearing 2,2-dialkyl substituents (Scheme 5). *S*-[3-(Trifluoromethyl)homoallyl] thioacetates **8** were prepared by the Mitsunobu reaction of homoallyl alcohols **4**.[20] Treatment with AcSH, DEAD, and PPh_3 afforded **8a**,**b** in moderate yields (Scheme 6).

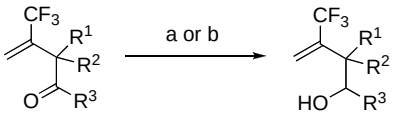
3-(Trifluoromethyl)homoallyl-substituted malonate and malononitrile **10** and **11** were prepared for carbocycle synthesis. Conjugate addition of 2-(trifluoromethyl)allylsilane[18] to diethyl

benzylidenemalonate **9** and a modified Mitsunobu reaction[21] of **4a** with malononitrile gave **10** and **11**, respectively (Scheme 7).



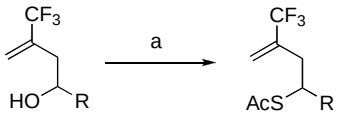
4a: R^1 = H, R^2 = Ph, Y = OH **5a** 89%
4b: R^1 = H, R^2 = C_6H_4-4-Br, Y = OH **5b** 65%
4c: R^1 = H, R^2 = 2-furyl, Y = OH **5c** 29%
4d: R^1 = H, R^2 = *n*-C_6H_{13}, Y = OH **5d** 61%
4e: R^1 = Ph, R^2 = H, Y = OH **5e** 64%
4f: R^1 = H, R^2 = H, Y = OTs **5f** 81%

Scheme 4. Preparation of *N*-[3-(Trifluoromethyl)homoallyl] Sulfonamides **5**. *Reagents and conditions*: (a) PPh_3 (1.5 equiv), DEAD (1.5 equiv), NHTsBoc (1.3 equiv), rt, 6 h, THF (for **4a**–**e**). (b) NaH (1.3 equiv), NHTsBoc (1.4 equiv), 90 °C, 4 h, DMF (for **4f**). (c) TFA (10 equiv), rt, 10 h, CH_2Cl_2.



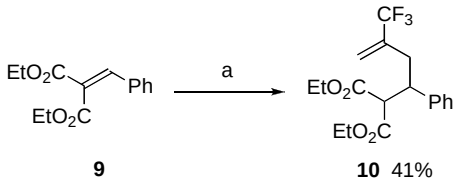
6a: R^1 = Me, R^2 = Me, R^3 = Ph **7a** 87%
6b: R^1, R^2 = -$(CH_2)_4$-, R^3 = Ph **7b** 86%
6c: R^1 = Me, R^2 = Me, R^3 = $(CH_2)_2C_6H_5$ **7c** 83%
6d: R^1 = Me, R^2 = Me, R^3 = CH=CHPh(E) **7d** 77%

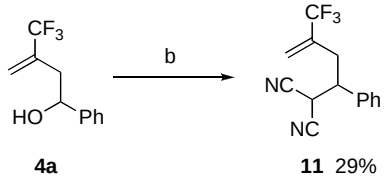
Scheme 5. Preparation of 3-(Trifluoromethyl)homoallyl Alcohols **7.** *Reagents and conditions*: (a) $NaBH_4$ (1.5 equiv), reflux, 3–4 h, EtOH (for **6a**–**c**). (b), $CeCl_3$ (1.0 equiv), $NaBH_4$ (1.0 equiv), 0 °C, 3 h, MeOH (for **6d**).



4a: R = Ph **8a** 34%
4d: R = *n*-C_6H_{13} **8b** 51%

Scheme 6. Preparation of *S*-[3-(Trifluoromethyl)homoallyl] Thioacetates **8**. *Reagents and conditions*: (a) PPh_3 (2.0 equiv), DEAD (2.0 equiv), AcSH (1.5 equiv), 0 °C, 12 h, THF.



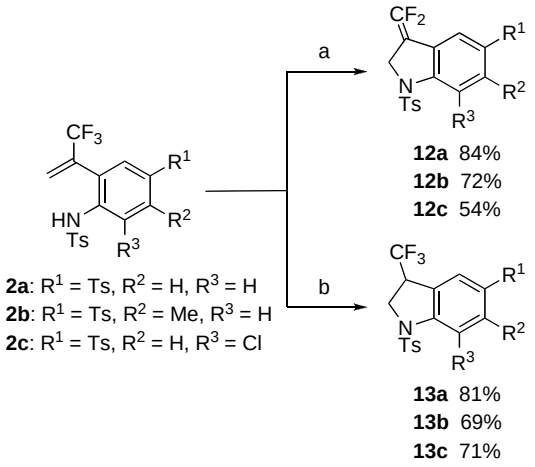


Scheme 7. Preparation of 3-(Trifluoromethyl)homoallyl-Substituted Malonate and Malononitrile **10** and **11**. *Reagents and conditions*: (a) $CH_2=C(CF_3)CH_2Si(CH_3)_3$ (1.0 equiv), TBAF (0.12 equiv), MS4Å, rt, 12 h, THF. (b) *n*-Bu_3P=CHCN (1.5 equiv), malononitrile (1.5 equiv), rt, 24 h, benzene.

Synthesis of Indolines and Indoles Bearing Fluorinated One-Carbon Units

We first examined the reaction of sulfonanilides **2** as precursors of indolines. The cyclization of **2a** was attempted by treatment with 1.2 equiv of NaH in several solvents. While the reaction in THF or 1,4-dioxane gave no cyclized products, the use of DMF successfully promoted the desired 5-*endo-trig* cyclization via an S_N2' reaction to afford 3-(difluoromethylene)indoline **12a** in 84% yield (Scheme 8).[16,22] On the other hand, a similar reaction of **2a** conducted in the presence of a proton source was expected to afford the addition product, 3-(trifluoromethyl)indoline **13a**.[16,23,24] The cyclization was examined by employing DBU instead of NaH as a base, where the sulfonamide NH group of **2a** and/or DBU•H^+ acted as a proton donor. Whereas 1 equiv of DBU gave 3-(trifluoromethyl)indoline **13a** only in 18% yield, 0.3 equiv of DBU surprisingly improved the yield of **13a** to 81% (Scheme 8). When this reaction was monitored by ^{19}F NMR after heating at 80 °C for 2 h, the formation of **12a** and **13a** was observed. The mixture, when heated at 120 °C, finally gave rise to **13a**. These facts indicate that DBU•HF acted as an HF source, which transformed **12a** to the trifluoromethylated indoline **13a** during the reaction.

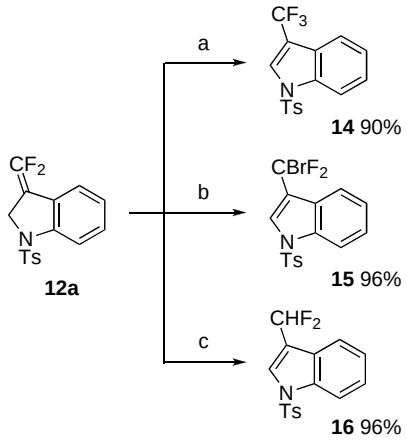
These two types of 5-*endo-trig* products, the S_N2' and the addition products, were also obtained from other sulfonamides **2b**,**c** bearing a methyl or a chlorine group on the benzene ring. The corresponding *o*-nitrobenzenesulfonamides (nosylamides)[25] also underwent these reactions, albeit slightly less effectively. Thus, indolines **12** and **13** bearing a difluoromethylene or trifluoromethyl group were selectively obtained from common substrates **2** by choosing the base and the reaction conditions (Scheme 8).



Scheme 8. Synthesis of 3-Difluoromethylene and 3-Trifluoromethyl Indolines **12** and **13**. *Reagents and conditions*: (a) NaH (1.2 equiv), 80 °C, 5–7 h, DMF. (b) DBU (0.3 equiv), 120 °C, 0.5–1 h, DMF.

Derivatization of indoline **12a** was examined in order to synthesize indoles bearing fluorinated one-carbon units. An attempted double bond isomerization leading to aromatization of **12a** failed under acidic (camphor sulfonic acid) and basic (DBU) conditions.[22] We then tried addition of electrophiles (XY) such as IF, Br_2, and HI to the exocyclic double bond of **12a**. Subsequent elimination of HX including an H at the 2-position from the adducts would allow the desired aromatization (Scheme 9). When **12a** was treated with 2.4 equiv of *N*-iodosuccinimide (NIS) and 2.5 equiv of Et_3N•3HF,[26] addition of IF followed by elimination of HI readily

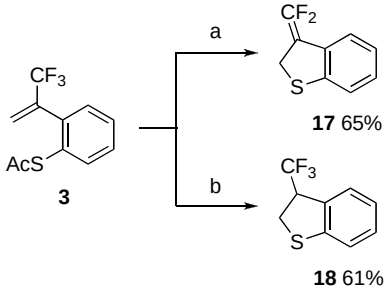
occurred to give 3-(trifluoromethyl)indole **14** in 90% yield. Similarly, treatment of **12a** with 1.3 equiv of Br_2 gave 3-(bromodifluoromethyl)indole **15** in 96% yield. Furthermore, when HI [generated from NaI (1.6 equiv), TMSCl (1.6 equiv), and H_2O (0.8 equiv)][27] was added to **12a**, 3-(difluoromethyl)indole **16** was obtained in 96% yield.[28] While the opposite regioselectivity in the HI addition of **12a** would be kinetically favorable because of the α-cation-stabilizing effect of fluorine,[29] the addition product with that regiochemistry underwent elimination of HI to regenerate **12a**. Consequently, the synthesis of indoles **14**–**16** with a variety of fluorinated one-carbon units is readily accomplished from a common starting material, **12a**.



Scheme 9. Synthesis of Indoles **14**–**16** Bearing Fluorinated One-Carbon Units. *Reagents and conditions*: (a) NIS (2.4 equiv), Et_3N•3HF (2.5 equiv), –10 °C, 2 h, CH_2Cl_2. (b) Br_2 (1.3 equiv), rt, 3 h, CCl_4. (c) NaI (1.6 equiv), TMSCl (1.6 equiv), H_2O (0.8 equiv), rt, 10 h, CH_3CN.

Synthesis of 2,3-Dihydrobenzo[*b*]thiophenes Bearing Fluorinated One-Carbon Units

As a further example of the intramolecular cyclization, we examined a sulfur nucleophile, although 5-*endo*-*trig* cyclizations with sulfur nucleophiles are not a disfavored process by Baldwin's rules because of the large atom size of sulfur.[1] A solution of a thiophenolate, generated in situ by treatment of thiophenol ester **3** with 1.1 equiv of potassium *tert*-butoxide (KO*t*-Bu) in THF, was heated at reflux to afford 3-difluoromethylene-2,3-dihydrobenzothiophene **17** in 65% yield (Scheme 10). The intramolecular addition process of the sulfur nucleophile under protic conditions was also examined. On treatment of **3** with 1.1 equiv of K_2CO_3 in MeOH, the desired 3-trifluoromethyl-2,3-dihydrobenzothiophene **18** was obtained in 61% yield (Scheme 10).[30] These cyclizations of sulfur nucleophiles proceeded under milder conditions than those required for nitrogen nucleophiles.



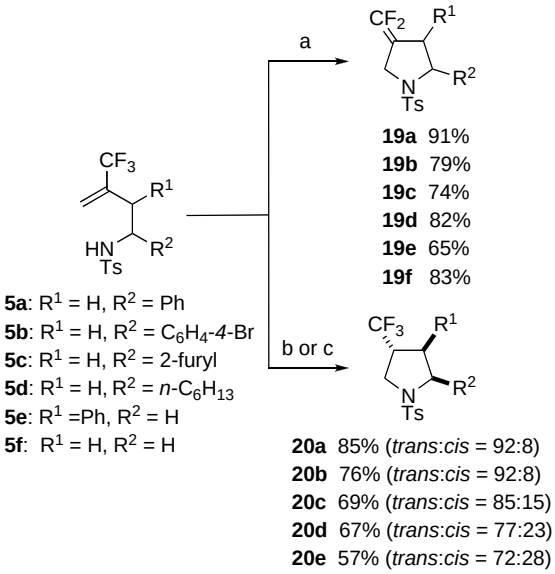
Scheme 10. Synthesis of 3-Difluoromethylene and 3-Trifluoromethyl 2,3-Dihydrobenzo[*b*]thiophenes **17** and **18**. *Reagents and conditions*: (a) KO*t*-Bu (1.1 equiv), reflux, 2 h, THF. (b) K_2CO_3 (1.1 equiv), reflux, 1 h, MeOH.

Synthesis of Pyrrolidines Bearing Fluorinated One-Carbon Units

Substrates **2** and **3** have a benzene ring tethering the nucleophilic heteroatom and the 1-(trifluoromethyl)vinyl group, which could allow a 6π-electrocyclization process to operate. To rule out the possibility of the 6π-electrocyclization mechanism and to broaden the scope for these types of 5-*endo*-*trig* cyclizations, we investigated the reaction of a nonconjugated system, *N*-[3-(trifluoromethyl)homoallyl] sulfonamides **5** bearing a two-sp^3 carbon tether. Whereas the 1-(trifluoromethyl)vinyl system without a 1-aryl group is known to possess a reduced S_N2' reactivity,[6b] we expected activation of the substrates by conducting the reactions in an intramolecular fashion.

Treatment of **5a** with 1.3 equiv of NaH in DMF successfully promoted a similar cyclization to afford 4-(difluoromethylene)pyrrolidine **19a** in 91% yield (Scheme 11).[15,16,31] In contrast, the intermolecular reaction of 5-phenyl-2-(trifluoromethyl)pent-1-ene with 4-methyl-*N*-propylbenzenesulfonamide gave only 2% yield of the corresponding S_N2' product under similar reaction conditions. These results clearly indicate that (i) the reactions proceeds via the nucleophilic 5-*endo*-*trig* cyclization, not via the electrocyclization, and (ii) substrate **5a** preserves good S_N2' reactivity due to the intramolecular nature of the reaction. We further examined the intramolecular S_N2' reaction of several other *N*-[3-(trifluoromethyl)homoallyl] sulfonamides **5b**–**e** bearing a 1-aryl, 1-alkyl, or 2-aryl group, and 1,2-unsubstituted homoallyl sulfonamide **5f**. The reactions afforded good to excellent yields of the desired 4-difluoromethylene-substituted pyrrolidines **19b**–**f**.

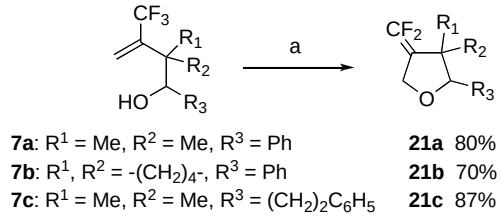
Cyclization of **5** in the presence of a proton source was attempted for the synthesis of (trifluoromethyl)pyrrolidines. In contrast to (trifluoromethyl)indoline synthesis, treatment of **5a** with DBU in DMF promoted the S_N2' reaction and not the addition reaction. When the reaction was conducted with 5 equiv of KOH in ethylene glycol or ethylene glycol–THF (10:1), the desired addition product, 4-(trifluoromethyl)pyrrolidine **20a**, was obtained in 85% yield with high 2,4-*trans* selectivity (*trans* : *cis* = 92 : 8) (Scheme 11).[15,16,32] We conducted the intramolecular addition reaction of other sulfonamides **5b**–**e**, which afforded good to high yields of the desired 4-(trifluoromethyl)pyrrolidines **20b**–**e** with 2,4-*trans* selectivity (**20b**–**d**)[33] or 3,4-*trans* selectivity (**20e**).[34] Under the cyclization conditions, neither the *cis* nor the *trans* isomer of **20b** underwent *cis*/*trans* isomerization, which indicates that the ratios represent the kinetic selectivity of the cyclization.



Scheme 11. Synthesis of 4-Difluoromethylene- and 4-Trifluoromethyl Pyrrolidines **19** and **20**. *Reagents and conditions*: (a) NaH (1.3 equiv), 120–130 °C, 0.5–4 h, DMF. (b) KOH (5 equiv), 130 °C, 20 h, $(CH_2OH)_2$ (for **20a**–**c** and **20e**). (c) KOH (5 equiv), 130 °C, 20 h, $(CH_2OH)_2$–THF (10:1) (for **20d**).

Synthesis of Tetrahydrofurans Bearing a Difluoromethylene Group

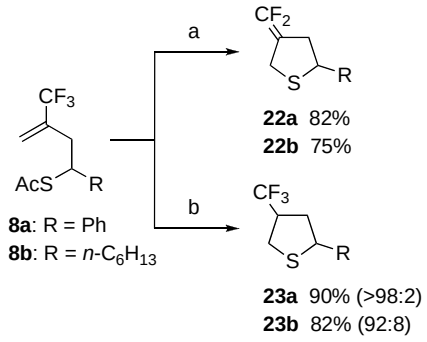
We then focused on the construction of oxygen heterocycles. An attempted S$_N$2′-type cyclization of homoallyl alcohol **4a** resulted in its intramolecular dehydration without accompanying cyclized products. Thus, we examined substrates **7** bearing two alkyl groups at the allylic position to prevent dehydration and to take advantage of the *gem*-dialkyl effect in cyclization.[35] On treatment with KO*t*-Bu in THF at 70 °C, homoallyl alcohols **7a**–**c** underwent an S$_N$2′-type reaction, leading to 4-difluoromethylene-substituted tetrahydrofurans **21a**–**c** in high yields (Scheme 12).[36] The 1-styryl-substituted substrate **7d** [R^1 = R^2 = Me, R^3 = CH=CHPh(*E*)], however, gave a complex mixture presumably due to 3,3-sigmatropic rearrangement. The reaction of **7a** with KO*t*-Bu, even when conducted in *t*-BuOH, gave **21a** as well as 4-(trifluoromethyl)tetrahydrofuran.



Scheme 12. Synthesis of 4-Difluoromethylene Tetrahydrofurans **21**. *Reagents and conditions*: (a) KO*t*-Bu (1.3 equiv), 70 °C, 2.5–6 h, THF.

Synthesis of Tetrahydrothiophenes Bearing Fluorinated One-Carbon Units

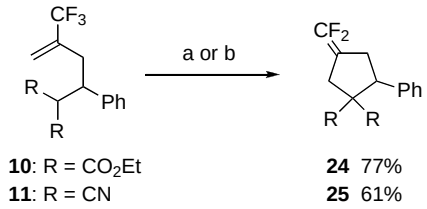
A sulfur nucleophile was employed in the cyclizations for the construction of the tetrahydrothiophene ring. Treatment of thioacetates **8a**,**b** with 1.3 equiv of NaOMe in DMF generated the corresponding thiolate, which underwent an S$_N$2′-type reaction to afford 4-(difluoromethylene)tetrahydrothiophenes **22a**,**b** in 82% and 75% yield, respectively (Scheme 13).[37] The addition reaction of **8a**,**b** was also readily effected on treatment with 1.1 equiv of K_2CO_3 in MeOH as a proton source (Scheme 13). The desired 4-(trifluoromethyl)tetrahydrothiophenes **23a**,**b** were obtained in 90% and 82% yield, respectively.[38]



Scheme 13. Synthesis of 3-Difluoromethylene and 3-Trifluoromethyl Tetrahydrothiophenes **22** and **23**. *Reagents and conditions*: (a) NaOMe (1.3 equiv), 100 °C, 10–15 h, DMF. (b) K_2CO_3 (1.1 equiv), reflux, 1–2 h, MeOH.

Synthesis of Cyclopentanes Bearing a Difluoromethylene Group

Having accomplished heterocycle synthesis, we turned our attention to the 5-*endo*-*trig* cyclization of 1-(trifluoromethyl)vinyl compounds with carbon nucleophiles, which would allow the construction of five-membered carbocycles with a fluorinated one-carbon unit. When 3-(trifluoromethyl)homoallyl-substituted malonate and malononitrile **10** and **11** were treated with 1.3 equiv of NaH in DMF, the S$_N$2′-type cyclization successfully proceeded to give difluoromethylene-substituted cyclopentanes **24** and **25** in 77% and 61% yield, respectively (Scheme 14).[39]



Scheme 14. Synthesis of Difluoromethylene Cyclopentanes **24** and **25**. *Reagents and conditions*: (a) KH (1.6 equiv), 110 °C, 3 h, DMF (for **10**). (b) NaH (1.3 equiv), 100 °C, 3 h, DMF (for **11**).

Conclusion

In conclusion, we have found that the 1-(trifluoromethyl)vinyl system with a nucleophilic moiety constitutes a new class of compounds that undergoes the normally disfavored 5-*endo*-*trig* cyclization. These '*anti*-Baldwin' results, based on the intramolecular substitution and addition concept, provide a high-yielding process for a variety of five-membered heterocycles and carbocycles. The resulting indolines, indoles, pyrrolidines, tetrahydrofurans, 2,3-dihydrobenzo[*b*]thiophenes, tetrahydrothiophenes, and cyclopentanes bearing fluorinated one-carbon units (=CF_2, CF_3, CHF_2, and $CBrF_2$) have so far been less accessible, despite their increasing and potential utility as agrochemicals, pharmaceuticals, and other materials. The

intramolecular substitution and addition concept opens the way to these fluorinated cyclic compounds.

Experimental Section

General: IR spectra were recorded by ATR (attenuated total reflectance) method. NMR spectra were recorded in $CDCl_3$ at 500 MHz (^{1}H NMR), 126 MHz (^{13}C NMR), and 470 MHz (^{19}F NMR). Chemical shift values were given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ 0.00), $CDCl_3$ (for ^{13}C NMR: δ 77.0), and C_6F_6 (for ^{19}F NMR: δ_F 0.0). Column chromatography and preparative thin-layer chromatography (PTLC) were performed on silica gel. All reactions were conducted under argon. Toluene, *N*,*N*-dimethylformamide (DMF), CH_2Cl_2, THF, and diethylether (Et_2O) were dried by passing over a column of activated alumina (A-2, Purity) followed by a column of Q-5 scavenger (Engelhard). MeOH, ethane-1,2-diol, and EtOH was distilled from Na, and stored over molecular sieves 3Å. Acetonitrile (CH_3CN) was distilled from P_2O_5 and then from CaH_2, and stored over molecular sieves 3Å. Pyridine was distilled from KOH, and stored over molecular sieves 4Å. Benzene was distilled to remove water azeotropically, and stored over molecular sieves 4Å. 2-(3,3,3-Trifluoroprop-1-en-2-yl)aniline (**1**),[17] [2-(trifluoromethyl)prop-2-en-1-yl]trimethylsilane,[18] 3-(trifluoromethyl)homoallyl alcohols **4**,[18,19] *tert*-butyl *N*-(4-methylbenzenesulfonyl)carbamate,[40] methyl trifluoromathanesulfonate,[41] and cyano(tributylphosphaniumyl)methanide (Bu_3P=CHCN)[21] were prepared according to the literature.

Preparation of 4-methyl-*N*-[2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]benzenesulfonamides (2): To a solution of 2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (**1**) (0.5 mmol) in pyridine (2.5 mL) was added 4-methylbenzenesulfonyl chloride (TsCl, 0.6 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP, 0.1 mmol) at 0 °C. The reaction mixture was stirred for 3 h at rt. The reaction was quenched with phosphate buffer (pH 7, 10 mL). Organic materials were extracted with EtOAc (10mL × 3). The combined extracts were washed with aqueous HCl (10 mL), brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography to give **2**.

4-Methyl-*N*-[2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]benzenesulfonamide (2a): Colorless crystals; yield 84%; IR (neat): 3282, 1495, 1412, 1346, 1188, 1130, 916, 812, 771, 669 cm^{-1}; ^{1}H NMR: δ = 2.38 (3H, s), 5.07 (1H, q, J_{HF} = 1.4 Hz), 6.07 (1H, q, J_{HF} = 1.4 Hz), 6.42 (1H, br s), 7.10–7.12 (2H, m), 7.23 (2H, d, J = 8.3 Hz), 7.32–7.36 (1H, m), 7.64 (2H, d, J = 8.3 Hz), 7.66 (1H, d, J = 8.4 Hz); ^{13}C NMR: δ = 21.5, 121.1, 122.4 (q, J_{CF} = 274 Hz), 124.6, 124.9, 125.5 (q, J_{CF} = 5 Hz), 127.3, 129.6, 130.2, 130.5, 134.6 (q, J_{CF} = 32 Hz), 134.8, 136.1, 144.2; ^{19}F NMR: δ_F = 94.4 (br s); elemental analysis: calcd (%) for $C_{16}H_{14}F_3NO_2S$: C 56.30, H 4.13, N 4.10, found: C 56.49, H 4.29, N 3.97.

4-Methyl-*N*-[4-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]benzenesulfonamide (2b): Colorless crystals; yield 87%; IR (neat): 3286, 1601, 1496, 1392, 1342, 1161, 1132, 904, 727 cm^{-1}; ^{1}H NMR: δ = 2.28 (3H, s), 2.38 (3H, s), 4.97 (1H, q, J_{HF} = 1.2 Hz), 6.00 (1H, q, J_{HF} = 1.2 Hz), 6.45 (1H, s), 6.91 (1H, s), 7.14 (1H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.3 Hz), 7.53 (1H, d, J = 8.4 Hz), 7.61 (2H, d, J = 8.3 Hz); ^{13}C NMR: δ = 20.6, 21.4, 122.0, 122.4 (q, J_{CF} = 274 Hz), 125.2 (q, J_{CF} = 5 Hz), 125.5, 127.3, 129.6, 130.8, 130.9, 132.1, 134.7 (q, J_{CF} = 32 Hz), 134.8, 136.3, 144.0; ^{19}F NMR: δ_F = 94.6 (br s); elemental analysis: calcd (%) for $C_{17}H_{16}F_3NO_2S$: C 57.46, H 4.54, N 3.94, found: C 57.42, H 4.78, N 3.69.

***N*-[5-Chloro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]-4-methylbenzenesulfonamide (2c):** Colorless crystals; yield 92%; IR (neat): 3388, 3282, 1597, 1493, 1389, 1342, 1163, 1122, 1092 cm^{-1}; ^{1}H NMR: δ = 2.40 (3H, s), 5.15 (1H, q, J_{HF} = 1.2 Hz), 6.12 (1H, q, J_{HF} = 1.2 Hz), 6.68 (1H, br s), 7.04 (1H, d, J = 8.3 Hz), 7.08 (1H, dd, J = 8.3, 1.9 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.67 (2H, d, J = 8.4 Hz), 7.70 (1H, d, J = 1.9 Hz); ^{13}C NMR: δ = 21.5, 120.6, 122.1 (q, J_{CF} = 274 Hz), 122.6, 124.6, 126.3 (q, J_{CF} = 5 Hz), 127.3, 129.8, 131.4, 133.7 (q, J_{CF} = 32 Hz), 135.6, 136.0, 136.1, 144.6; ^{19}F NMR: δ_F = 94.3 (br s); HRMS (FAB): calcd for $C_{16}H_{14}ClF_3NO_2S$ ([M + H]$^+$) 376.0386, found 376.0381.

***S*-[2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl] ethanethioate (3):** To a solution of 2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (**1a**) (522 mg, 2.79 mmol) in CH_3CN (8 mL) were added trifluoroacetic acid (TFA, 0.43 mL, 5.6 mmol) and 3-methylbutyl nitirite (*i*-AmONO, 0.75 mL, 5.6 mmol) at 0 °C. The reaction mixture was stirred for 0.5 h. The solution was treated with AcSNa [prepared from thioacetic *S*-acid (AcSH, 0.60 mL, 8.4 mmol) and sodium hydride (NaH, 60 % dispersion in mineral oil; 335 mg, 8.4 mmol) in DMF (5 mL) at 0 °C], and stirred for 3 h at rt. The reaction was quenched with phosphate buffer (pH 7, 10 mL). The mixture was filtered through Celite, and then organic materials were extracted with Et_2O (15 mL × 3). After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **3** (214 mg, 31%) as a pale yellow liquid. IR (neat): 1705, 1473, 1402, 1346, 1171, 1111, 1093, 906, 729 cm^{-1}; ^{1}H NMR: δ = 2.38 (3H, s), 5.52 (1H, s), 6.06 (1H, s), 7.36–7.38 (1H, m), 7.43–7.45 (2H, m), 7.51–7.53 (1H, m); ^{13}C NMR: δ = 30.0, 122.6 (q, J_{CF} = 274 Hz), 123.5 (q, J_{CF} = 5 Hz), 128.1, 129.6, 129.8, 130.7, 136.8, 137.2 (q, J_{CF} = 33 Hz), 138.2, 193.4; ^{19}F NMR: δ_F = 95.1 (br s); HRMS (FAB): calcd for $C_{11}H_{10}F_3OS$ ([M + H]$^+$) 247.0404, found 247.0415.

Preparation of 4-methyl-*N*-[3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamides (5):

To a solution of 3-(trifluoromethyl)but-3-en-1-ol (**4**) (2.0 mmol), triphenylphosphine (PPh_3, 1.05 g, 4.00 mmol), and *tert*-butyl *N*-(4-methylbenzenesulfonyl)carbamate (814 mg, 3.00 mmol) in THF (10 mL) was added diethyl azodicarboxylate (DEAD, 40% in toluene; 1.36 mL, 4.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give *tert*-butyl *N*-(4-methylbenzenesulfonyl)-*N*-[3-(trifluoromethyl)but-3-en-1-yl]carbamate. To a solution of *tert*-butyl *N*-(4-methylbenzenesulfonyl)-*N*-[3-(trifluoromethyl)but-3-en-1-yl]carbamate (1.5 mmol) in CH_2Cl_2 (15 mL) was added TFA (15 mmol) at rt. The reaction mixture was stirred at rt for 10 h. The reaction was quenched with aqueous Na_2CO_3 (20 mL), and organic materials were extracted with CH_2Cl_2 (15 mL × 3). The combined extracts were washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give **5**.

4-Methyl-*N*-[1-phenyl-3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide (5a): Colorless crystals; yield 89%; m.p. 78–80 °C; IR (neat): 3269, 3064, 3030, 2927, 1456, 1325, 1159, 1120, 912 cm^{-1}; ^{1}H NMR: δ = 2.37 (3H, s), 2.58 (1H, dd, J = 15.3, 7.2 Hz), 2.71 (1H, dd, J = 15.3, 7.8 Hz), 4.49 (1H, ddd, J = 7.8, 7.3, 7.2 Hz), 4.91 (1H, br s), 5.19 (1H, s), 5.63 (1H, s), 7.02–7.04 (2H, m), 7.14 (2H, d, J = 8.2 Hz), 7.17–7.19 (3H, m), 7.54 (2H, d, J =8.2 Hz); ^{13}C NMR: δ = 21.4, 37.6, 56.5, 121.9 (q, J_{CF} = 5 Hz), 123.3 (q, J_{CF} = 272 Hz), 126.6, 127.1, 127.8, 128.6, 129.3, 133.4 (q, J_{CF} = 30 Hz), 137.2, 139.5, 143.2; ^{19}F NMR: δ_F = 93.4 (br s); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79, found: C 58.56, H 5.08, N 3.80.

***N*-[1-(4-Bromophenyl)-3-(trifluoromethyl)but-3-en-1-yl]-4-methylbenzenesulfonamide (5b):** Colorless crystals; yield 65%; m.p. 131–133 °C; IR (neat): 3263, 3066, 3030, 2924, 2872, 1489, 1321, 1155, 1117, 953 cm^{-1}; ^{1}H NMR: δ = 2.39 (3H, s), 2.49 (1H, dd, J = 15.2, 7.2 Hz), 2.64 (1H, dd, J = 15.2, 8.0 Hz), 4.46 (1H, ddd, J = 8.0, 7.6, 7.2 Hz), 5.21 (1H, s), 5.61 (1H, s), 5.91 (1H, br s), 6.90 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.1 Hz), 7.25 (2H, d, J = 8.1 Hz), 7.50 (2H, d, J =8.4 Hz); ^{13}C NMR: δ = 21.4, 37.4, 55.9, 121.6, 122.3 (q, J_{CF} = 6 Hz), 123.2 (q, J_{CF} = 272 Hz), 127.0, 128.4, 129.4, 131.5, 133.0 (q, J_{CF} = 30 Hz), 136.9, 138.4, 143.6; ^{19}F NMR: δ_F = 93.5 (br s); elemental analysis: calcd (%) for $C_{18}H_{17}BrF_3NO_2S$: C 48.23, H 3.82, N 3.12, found: C 48.14, H 3.77, N 2.89.

***N*-[1-(2-Furyl)-3-(trifluoromethyl)but-3-en-1-yl]-4-methylbenzenesulfonamide (5c):** Colorless crystals; yield 29%; IR (neat): 3269, 1599, 1326, 1157, 1114, 1011, 949 cm^{-1}; ^{1}H NMR: δ = 2.38 (3H, s), 2.66 (1H, dd, J = 15.1, 8.0 Hz), 2.70 (1H, dd, J = 15.1, 7.5 Hz), 4.61 (1H, ddd, J = 8.6, 8.0, 7.5 Hz), 5.24 (1H, s), 5.32 (1H, d, J = 8.6 Hz), 5.64 (1H, s), 5.92 (1H, d, J = 3.2 Hz), 6.10 (1H, dd, J = 3.2, 1.8 Hz), 7.16 (1H, d, J = 1.8 Hz), 7.19 (2H, d, J = 8.1 Hz), 7.61 (2H, d, J = 8.1 Hz); ^{13}C NMR: δ = 21.4, 35.0, 50.2, 107.8, 110.0, 121.9 (q, J_{CF} = 6 Hz), 123.3 (q, J_{CF} = 272 Hz), 127.0, 129.4, 132.1 (q, J_{CF} = 30 Hz), 137.3, 142.1, 143.3, 151.2; ^{19}F NMR: δ_F = 93.4 (br s); HRMS (FAB): calcd for $C_{16}H_{17}F_3NO_3S$ ([M + H]$^+$) 360.0881, found 360.0878.

4-Methyl-*N*-[2-(trifluoromethyl)dec-1-en-4-yl]benzenesulfonamide (5d): Colorless crystals; yield 61%; m.p. 65–67 °C; IR (neat): 3276, 3020, 2956, 2929, 2860, 1217, 1159, 1120 cm^{-1}; ^{1}H NMR: δ = 0.84 (3H, t, J = 7.1 Hz), 1.02–1.32 (9H, m), 1.42–1.50 (1H, m), 2.26 (1H, dd, J = 14.9, 7.3 Hz), 2.37 (1H, dd, J = 14.9, 6.6 Hz), 2.42 (3H, s), 3.37–3.44 (1H, m), 4.29 (1H, br s), 5.33 (1H, s), 5.66 (1H, s), 7.29 (2H, d, J = 8.3 Hz), 7.74 (2H, d, J = 8.3 Hz); ^{13}C NMR: δ = 14.0, 21.4, 22.4, 24.9, 28.7, 31.5, 34.3, 36.0, 52.4, 121.3 (q, J_{CF} = 6 Hz), 123.2 (q, J_{CF} = 272 Hz), 127.0, 129.5, 134.3 (q, J_{CF} = 29 Hz), 137.9, 143.3; ^{19}F NMR: δ_F = 93.6 (br s); elemental analysis: calcd (%) for $C_{18}H_{26}F_3NO_2S$: C 57.27, H 6.94, N 3.71, found: C 57.03, H 7.20, N 3.59.

4-Methyl-*N*-[2-phenyl-3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide (5e): Colorless crystals; yield 64%; m.p. 108–110 °C; IR (neat): 3282, 3032, 1417, 1325, 1159, 1124, 1093 cm^{-1}; ^{1}H NMR: δ = 2.44 (3H, s), 3.27 (1H, ddd, J = 13.1, 8.1, 5.3 Hz), 3.46 (1H, ddd, J = 13.1, 7.4, 7.1 Hz), 3.62 (1H, dd, J = 8.1, 7.4 Hz), 4.51 (1H, dd, J = 7.1, 5.3 Hz), 5.45 (1H, q, J_{HF} = 1.0 Hz), 5.90 (1H, q, J_{HF} = 1.0 Hz), 7.07 (2H, d, J = 8.1 Hz), 7.25–7.32 (5H, s), 7.68 (2H, d, J = 8.1 Hz); ^{13}C NMR: δ = 21.5, 44.6, 46.2, 119.9 (q, J_{CF} = 6 Hz), 123.2 (q, J_{CF} = 275 Hz), 127.0, 127.8, 127.8, 129.0, 129.8, 136.6, 137.5, 138.4 (q, J_{CF} = 29 Hz), 143.7; ^{19}F NMR: δ_F = 94.5 (br s); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79, found: C 58.72, H 5.05, N 3.54.

4-Methyl-*N*-[3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide (5f): To a solution of 3-(trifluoromethyl)but-3-en-1-yl 4-methylbenzenesulfonate (**4f**) (506 mg, 1.72 mmol) and *tert*-butyl *N*-(4-methylbenzenesulfonyl)carbamate (661 mg, 2.44 mmol) in DMF (10 mL) was added NaH (55% dispersion in mineral oil; 97 mg, 2.2 mmol) at 0 °C. After being stirred at that temperature for 0.5 h, the reaction mixture was heated at 90 °C for 4 h. The reaction was quenched with phosphate buffer (pH 7, 20 mL), and organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with brine (20 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, crude *tert*-butyl (4-methylbenzenesulfonyl)-*N*-[3-(trifluoromethyl)but-3-en-1-yl]carbamate (715 mg) was obtained. To a solution of crude *tert*-butyl *N*-(4-methylbenzenesulfonyl)-*N*-[3-(trifluoromethyl)but-3-en-1-yl]carbamate (715 mg) in CH_2Cl_2 (20 mL) was added TFA (1.5 mL, 20 mmol) at rt. After the mixture was stirred for 6 h, the reaction was quenched with aqueous $NaHCO_3$ (40 mL). Organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were washed with brine (20 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 2:1) to give **5f** (408 mg, 81%) as colorless crystals. m.p. 54–55 °C; IR (neat): 3263, 1427, 1315, 1153, 1117, 945, 928, 814 cm^{-1}; ^{1}H NMR: δ = 2.42 (2H, t, J = 6.9 Hz), 2.44 (3H, s), 3.14 (2H, dt, J = 6.9, 6.9 Hz), 4.50 (1H, br s), 5.37 (1H, q, J_{HF} = 1.3 Hz), 5.76 (1H, q, J_{HF} = 1.4 Hz), 7.33 (2H, d, J = 8.1 Hz), 7.75 (2H, d, J = 8.1 Hz); ^{13}C NMR: δ = 21.5, 30.2, 41.0, 120.9 (q, J_{CF} = 6 Hz), 123.3 (q, J_{CF} = 274 Hz), 127.0, 129.8, 134.4 (q, J_{CF} = 30 Hz), 136.7, 143.7; ^{19}F NMR: δ_F = 93.3 (br s); elemental analysis: calcd (%) for $C_{12}H_{14}F_3NO_2S$: C 49.14, H 4.81, N 4.78, found: C 49.27, H 4.96, N 4.59.

1-Phenyl-3-(trifluoromethyl)but-3-en-1-one (26): To a mixture of pyridinium chlorochromate (38.4 g, 178 mmol) and silica gel (38.4 g) in CH_2Cl_2 (350 mL) was added 1-phenyl-3-(trifluoromethyl)but-3-en-1-ol (**4a**) (13.9 g, 64.4 mmol). The reaction mixture was stirred for 2 h at rt, and then diluted with Et_2O. The solid materials were removed by filtration through a short column of Florisil. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 4:1) to give **26** (12.2 g, 88%) as colorless crystals. IR (neat): 3062, 1689, 1414, 1358, 1323, 1169, 1115, 1005, 949, 754, 688 cm^{-1}; ^{1}H NMR: δ = 3.85 (2H, s), 5.51 (1H, br s), 5.95 (1H, br s), 7.48 (2H, dd, J = 7.7, 7.7 Hz), 7.60 (1H, t, J = 7.7 Hz), 7.96 (2H, d, J = 7.7 Hz); ^{13}C NMR: δ = 38.7, 122.6 (q, J_{CF} = 6 Hz), 123.1 (q, J_{CF} = 272 Hz), 128.3, 128.7, 131.8 (q, J_{CF} = 31 Hz), 133.5, 135.9, 194.8; ^{19}F NMR: δ_F = 92.9 (br s); elemental analysis: calcd (%) for $C_{11}H_9F_3O$: C 61.68, H 4.24, found: C 61.75, H 4.39.

2-Methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (27): To a solution of 1-phenyl-3-(trifluoromethyl)but-3-en-1-one (**26**) (500 mg, 2.33 mmol) in Et_2O (20 mL) was added a solution of potassium hexamethyldisilazide (KHMDS, 0.56 M in toluene;

4.1 mL, 2.3 mmol) dropwise, and the reaction mixture was stirred for 40 min at –78 °C. Methyl trifluoromethanesulfonate (0.26 mL, 2.3 mmol) was added at that temperature, and then the mixture was allowed to warm up to rt. After stirring for 6 h, reaction was quenched with phosphate buffer (pH 7, 20 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (hexane–EtOAc, 4:1) to give **27** (429 mg, 81%) as a colorless liquid. IR (neat): 2987, 2943, 1687, 1273, 1219, 1169, 1115, 962, 704, 687 cm^{-1}; ^1H NMR: δ = 1.42 (3H, d, J = 6.8 Hz), 4.36 (1H, q, J = 6.8 Hz), 5.52 (1H, br s), 5.87 (1H, br s), 7.47 (2H, dd, J = 7.2, 7.2 Hz), 7.58 (1H, t, J = 7.2 Hz), 7.90 (2H, d, J = 7.2 Hz); ^{13}C NMR: δ = 17.8, 40.2, 120.7 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 272 Hz), 128.4, 128.7, 133.3, 135.5, 137.9 (q, J_{CF} = 30 Hz), 198.5; ^{19}F NMR: δ_F = 94.0 (br s); elemental analysis: calcd (%) for $C_{12}H_{11}F_3O$: C 63.16, H 4.86, found: C 63.13, H 5.05.

2,2-Dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (6a): To a solution of 2-methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (**27**) (205 mg, 0.90 mmol) in Et_2O (10 mL) was added a solution of KHMDS (0.56 M in toluene; 1.6 mL, 0.90 mmol) dropwise, and the reaction mixture was stirred for 1 h at –78 °C. Methyl trifluoromethanesulfonate (0.11 mL, 0.90 mmol) was added at that temperature, and then the mixture was allowed to warm up to rt. After stirring for 12 h, reaction was quenched with phosphate buffer (pH 7, 10 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **6a** (110 mg, 51%) as a colorless liquid. IR (neat): 2987, 1684, 1323, 1246, 1178, 1119, 1092, 972, 719, 690 cm^{-1}; ^1H NMR: δ = 1.53 (6H, s), 5.60 (1H, br s), 5.93 (1H, br s), 7.38 (2H, dd, J = 8.0, 8.0 Hz), 7.48 (1H, t, J = 8.0 Hz), 7.85 (2H, d, J = 8.0 Hz); ^{13}C NMR: δ = 26.4, 49.8, 120.4 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 276 Hz), 128.1, 129.2, 132.1, 135.6, 143.5 (q, J_{CF} = 27 Hz), 200.8; ^{19}F NMR: δ_F = 100.3 (br s); elemental analysis: calcd (%) for $C_{13}H_{13}F_3O$: C 64.46, H 5.41, found: C 64.25, H 5.58.

Phenyl[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclopentyl]methanone (6b): To a solution of 1-phenyl-3-(trifluoromethyl)but-3-en-1-one (**4a**) (1.29 g, 6.0 mmol) in Et_2O (30 mL) was added a solution of KHMDS (0.50 M in toluene; 12.6 mL, 6.3 mmol) dropwise at –78 °C. The reaction mixture was stirred for 10 min at 0 °C, and was transferred to a solution of 1,4-diiodobutane (4.7 mL, 36 mmol) and hexamethylphosphoric triamide (HMPA, 10 mL) in Et_2O (30 mL) at –78 °C. The reaction mixture was allowed to warm up to rt, and stirred for 12 h. Reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1 to 5:1) to give a mixture of **6b** and 2-(4-iodobutyl)-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (1.82 g) as a colorless liquid. To a solution of the mixture (1.43 g) in Et_2O (30 mL) was added a solution of KHMDS (0.50 M in toluene; 7.22 mL, 3.6 mmol) dropwise at –78 °C. The reaction mixture was stirred for 5 min at –78 °C, and allowed to warm up to rt. After stirring for 4 h, the reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **6b** (0.90 g, 67% for 2 steps) as a colorless liquid. IR (neat): 2958, 2925, 2854, 1684, 1317, 1234, 1167, 1126 cm^{-1}; ^1H NMR: δ = 1.56–1.64 (2H, m), 1.67–1.76 (2H, m), 2.02 (2H, ddd, J = 13.0, 6.5, 6.5 Hz), 2.46 (2H, ddd, J = 13.0, 6.5, 6.5 Hz), 5.55 (1H, q, J_{HF} = 1.0 Hz), 5.87 (1H, q, J_{HF} = 0.9 Hz), 7.38 (2H, dd, J = 7.5, 7.5 Hz), 7.48 (1H, t, J = 7.5 Hz), 7.88 (2H, d, J = 7.5 Hz); ^{13}C NMR: δ = 24.3, 35.9, 60.7, 119.9 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 277 Hz), 128.1, 129.5, 132.2, 135.4, 142.1 (q, J_{CF} = 27 Hz), 199.2; ^{19}F NMR: δ_F = 99.9 (br s); HRMS (FAB): calcd for $C_{15}H_{16}F_3O$ ($[M + H]^+$) 269.1153, found 269.1178.

1-Phenyl-5-(trifluoromethyl)hex-5-en-3-one (28): To a mixture of pyridinium chlorochromate (13.6 g, 63.2 mmol) and silica gel (14 g) in dichloromethane (126 mL) was added 5-trifluoromethyl-1-phenylhex-5-en-3-ol (10.3 g, 42.2 mmol). The reaction mixture was stirred for 12 h at rt, and then diluted with Et_2O. The solid materials were removed by filtration through Celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–Et_2O, 5:1) to give **28** (9.81 g, 96%) as a colorless liquid. IR (neat): 3030, 2927, 1722, 1604, 1496, 1456, 1412, 1363, 1308, 1169, 1113, 950, 748, 698 cm^{-1}; ^1H NMR: δ = 2.82 (2H, t, J = 7.6 Hz), 2.92 (2H, t, J = 7.6 Hz), 3.25 (2H, s), 5.45 (1H, q, J_{HF} = 1.1 Hz), 5.89 (1H, q, J_{HF} = 1.5 Hz), 7.17–7.22 (3H, m), 7.29 (2H, dd, J = 7.6, 7.6 Hz); ^{13}C NMR: δ = 29.5, 43.2, 43.9, 122.7 (q, J_{CF} = 6 Hz), 123.0 (q, J_{CF} = 274 Hz), 126.2, 128.3, 128.5, 131.3 (q, J_{CF} = 31 Hz), 140.5, 204.2; ^{19}F NMR: δ_F = 92.7 (br s); elemental analysis: calcd (%) for $C_{13}H_{13}F_3O$: C 64.46, H 5.41, found: C 64.68, H 5.60.

4-Methyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (29): To a solution of 1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (**28**) (9.81 g, 40.5 mmol) in Et_2O (200 mL) was added a solution of KHMDS (0.70 M in toluene; 59.6 mL, 41.7 mmol) dropwise at –78 °C, and the reaction mixture was stirred for 1 h at that temperature. Methyl trilfluoromethanesulfonate (9.2 mL, 81 mmol) was added, and the mixture was stirred for 15 min. After being allowed to warm up to rt, the reaction mixture was stirred for 12 h. Reaction was quenched with phosphate buffer (pH 7, 50 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **29** (9.74 g, 94%) as a colorless liquid. IR (neat): 3030, 2983, 2941, 1720, 1604, 1496, 1454, 1415, 1304, 1277, 1171, 1115, 953, 748, 698 cm^{-1}; ^1H NMR: δ = 1.25 (3H, d, J = 7.0 Hz), 2.71–2.78 (1H, m), 2.81–2.90 (3H, m), 3.37 (1H, q, J = 7.0 Hz), 5.35 (1H, s), 5.80 (1H, s), 7.15–7.20 (3H, m), 7.27 (2H, dd, J = 7.5, 7.5 Hz); ^{13}C NMR: δ = 16.5, 29.7, 42.6, 45.7, 120.3 (q, J_{CF} = 6 Hz), 123.4 (q, J_{CF} = 274 Hz), 126.1, 128.3, 128.4, 137.6 (q, J_{CF} = 30 Hz), 140.7, 207.3; ^{19}F NMR: δ_F = 93.3 (br s); elemental analysis: calcd (%) for $C_{14}H_{15}F_3O$: C 65.62, H 5.90, found: C 65.84, H 6.13.

4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (6c): To a solution of 4-methyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (**29**) (5.72 g, 22.3 mmol) in Et_2O (200 mL) was added a solution of KHMDS (0.70 M in toluene; 33.5 mL, 23.4 mmol) dropwise at –105 °C, and the reaction mixture was stirred for 30 min at –90 °C. Methyl trifluoromethanesulfonate (5.05 mL, 44.6 mmol) was added at –105 °C, and the mixture was stirred for 10 min at that temperature. After being allowed to warm up to rt, the mixture was stirred for 2 h. Reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **6c** (4.38 g, 73%) as a colorless liquid. IR (neat): 3028, 2983, 2941, 1716, 1454, 1325, 1176, 1126, 1099, 953 cm^{-1}; ^1H NMR: δ = 1.31 (6H, s), 2.73 (2H, t, J = 7.6 Hz), 2.89 (2H, t, J = 7.6 Hz), 5.56 (1H, s), 5.91 (1H, s), 7.19 (2H, d, J = 7.5 Hz), 7.20 (1H, t, J = 7.5 Hz), 7.29 (2H, dd, J = 7.5, 7.5 Hz); ^{13}C NMR: δ = 23.5, 30.1, 38.7, 50.4, 120.8 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 126.0, 128.3, 128.4, 141.0, 142.4 (q, J_{CF} = 28 Hz), 209.1; ^{19}F NMR: δ_F = 100.3 (br s); HRMS (FAB): calcd for $C_{15}H_{18}F_3O$ ($[M + H]^+$) 271.1310, found 271.1281.

4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hexa-1,5-dien-3-one (6d): To a solution of 4,4-dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (**6c**) (2.71 g, 10 mmol) was added a solution of KHMDS (0.50 M in toluene; 21.1 mL, 10.5 mmol) dropwise at –78 °C, and the reaction mixture was stirred for 10 min at 0 °C. Trimethylsilyl chloride (2.6 mL, 20.1 mmol) was added at –78 °C, and the mixture was stirred for 15 min. After being allowed to warm up to rt, reaction was quenched with phosphate buffer (pH 7, 50 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude silyl enolate was obtained as pale brown liquid. Then, the crude product was dissolved into CH_3CN (20 mL), and the solution was added to a solution of $Pd(OAc)_2$ (2.9 g, 13mmol) in CH_3CN (20 mL) at rt. After stirred for 12 h at rt, Et_2O (50 mL) was added, and the solid materials were removed through Celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1 to 5:1) to give **6d** (1.91 g, 71%) as a colorless liquid. IR (neat): 2983, 2941, 1689, 1610, 1323, 1176, 1120, 1099, 1053, 982, 953 cm^{-1}; ^1H NMR: δ = 1.42 (6H, s), 5.68 (1H, s), 6.00 (1H, s), 6.91 (1H, d, J = 15.7 Hz), 7.37–7.38 (3H, m), 7.53 (2H, dd, J = 3.2, 3.2 Hz), 7.72 (1H, d, J = 15.7 Hz); ^{13}C NMR: δ = 23.8, 49.8, 120.2, 121.0 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 128.4, 128.8, 130.5, 134.5, 142.8 (q, J_{CF} = 28 Hz), 143.7, 198.6; ^{19}F NMR: δ_F = 100.2 (br s); elemental analysis: calcd (%) for $C_{15}H_{15}F_3O$: C 67.16, H 5.64, found: C 67.23, H 5.81.

Preparation of 2,2-dialkyl- 3-(trifluoromethyl)homoallyl alcohol (7): To a solution of 1-substituted 2,2-dialkyl-3-trifluoromethylbut-3-en-1-one (**6**) (1.45 mmol) in EtOH (14 mL) was added sodium borohydride (84 mg, 2.2 mmol) at rt. The reaction mixture was heated to reflux for 3 h, and then phosphate buffer (pH 7, 30 mL) was added to quench the reaction. The mixture was extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (hexane–EtOAc, 5:1) to give **7**.

2,2-Dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-ol (7a): A colorless liquid; yield 87%; IR (neat): 3464, 3064, 3022, 2987, 2924, 1454, 1321, 1115, 1092, 1039, 949, 727, 702 cm^{-1}; ^1H NMR: δ = 1.08 (3H, s), 1.19 (3H, s), 1.94 (1H, d, J = 2.8 Hz), 4.85 (1H, d, J = 2.8 Hz), 5.49 (1H, q, J_{HF} = 1.8 Hz), 5.92 (1H, q, J_{HF} = 1.2 Hz), 7.23–7.32 (5H, m); ^{13}C NMR: δ = 21.7, 23.8, 43.0, 77.7, 122.0 (q, J_{CF} = 7 Hz), 124.4 (q, J_{CF} = 277 Hz), 127.5, 127.6, 128.0, 140.2, 143.3 (q, J_{CF} = 27 Hz); ^{19}F NMR: δ_F = 100.9 (br s); elemental analysis: calcd (%) for $C_{13}H_{15}F_3O$: C 63.93, H 6.19, found: C 64.12, H 6.46.

Phenyl[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclopentyl]methanol (7b): A colorless liquid; yield 86%; IR (neat): 3464, 3064, 3032, 2962, 2879, 1454, 1301, 1159, 1115, 1078, 947, 704 cm^{-1}; ^1H NMR: δ = 1.50–1.59 (4H, m), 1.78–1.80 (1H, m), 1.88–1.94 (3H, m), 2.07 (1H, d, J = 3.0 Hz), 4.87 (1H, d, J = 3.0 Hz), 5.29 (1H, q, J_{HF} = 1.5 Hz), 5.86 (1H, q, J_{HF} = 1.2 Hz), 7.24–7.31 (5H, m); ^{13}C NMR: δ = 22.7, 22.8, 32.1, 32.6, 55.9, 76.6, 123.0 (q, J_{CF} = 7 Hz), 124.4 (q, J_{CF} = 277 Hz), 127.6, 127.6, 127.7, 141.1, 141.1 (q, J_{CF} = 26 Hz); ^{19}F NMR: δ_F = 101.8 (br s); HRMS (FAB): calcd for $C_{15}H_{18}F_3O$ ($[M + H]^+$) 271.1310, found 271.1308.

4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-ol (7c): A colorless liquid; yield 83%; IR (neat): 3456, 3028, 2981, 2929, 1319, 1153, 1117, 1092, 949, 748, 698 cm^{-1}; ^1H NMR: δ = 1.14 (3H, s), 1.19 (3H, s), 1.55 (1H, d, J = 5.2 Hz), 1.57–1.64 (1H, m), 1.74–1.82 (1H, m), 2.62 (1H, ddd, J = 13.6, 10.0, 6.8 Hz), 2.92 (1H, ddd, J = 13.6, 10.4, 5.2 Hz), 3.69 (1H, dd, J = 10.4, 5.2 Hz), 5.50 (1H, q, J_{HF} = 2.2 Hz), 5.88 (1H, d , J_{HF} = 0.8 Hz), 7.19–7.30 (5H, m); ^{13}C NMR: δ = 22.2, 23.4, 33.4, 33.4, 42.7, 75.5, 121.1 (q, J_{CF} = 7 Hz), 124.2 (q, J_{CF} = 277 Hz), 125.9, 128.4, 128.4, 142.0, 143.8 (q, J_{CF} = 26 Hz); ^{19}F NMR: δ_F = 101.3 (br s); HRMS (FAB): calcd for $C_{15}H_{20}F_3O$ ($[M + H]^+$) 273.1466, found 273.1473.

4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hexa-1,5-dien-3-ol (7d): To a solution of 4,4-dimethyl-1-phenyl-5-trifluoromethyl-hexa-1,5-dien-3-one (**6d**) (150 mg, 0.56 mmol) in MeOH (1.3 mL) was added cerium (III) chloride (140 mg, 0.57 mmol) and stirred at rt for 0.5 h. After cooling the mixture to 0 °C, sodium borohydride (21 mg, 0.56 mmol) was added to the mixture. The reaction mixture was stirred for 3 h, and then phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with ether three times. The combined organic extracts were washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (hexane–EtOAc, 5:1) to give **7d** (117 mg, 77%) as a colorless liquid. IR (neat): 3433, 3028, 2983, 2887, 1496, 1408, 1323, 1153, 1115, 1086, 968, 754, 692 cm^{-1}; ^1H NMR: δ = 1.20 (3H, s), 1.26 (3H, s), 1.77 (1H, br d, J = 3.0 Hz), 4.38 (1H, dd, J = 6.7, 3.0 Hz), 5.60 (1H, q, J_{HF} = 1.8 Hz), 5.94 (1H, q, J_{HF} = 1.2 Hz), 6.20 (1H, dd, J = 15.9, 6.7 Hz), 6.62 (1H, d, J = 15.9 Hz), 7.25 (1H, t, J = 7.2 Hz), 7.32 (2H, dd, J = 7.8, 7.2 Hz), 7.38 (2H, d, J = 7.8 Hz); ^{13}C NMR: δ = 22.5, 23.4, 42.6, 76.9, 121.6 (q, J_{CF} = 7 Hz), 124.3 (q, J_{CF} = 277 Hz), 126.5, 127.8, 127.8, 128.6, 132.7, 136.6, 143.3 (q, J_{CF} = 28 Hz); ^{19}F NMR: δ_F = 101.3 (br s); HRMS (FAB): calcd for $C_{15}H_{18}F_3O$ ($[M + H]^+$) 271.1310, found 271.1334.

***S*-[1-Phenyl-3-(trifluoromethyl)but-3-en-1-yl] ethanethioate (8a):** To a solution of 1-phenyl-3-(trifluoromethyl)but-3-en-1-ol (**4a**) (520 mg, 2.41 mmol), PPh_3 (1.90 g, 7.23 mmol), and thioacetic acid (0.345 mL, 3.6 mmol) in THF (15 mL) was added DEAD

(40% in toluene solution; 3.45 mL, 6.83 mmol) at –10 °C. The reaction mixture was stirred at 0 °C for 12 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 50:1) to give **8a** (224 mg, 34%) as a pale yellow liquid. IR (neat): 3064, 3032, 2929, 1693, 1217, 1169, 1124 cm^{-1}; ^1H NMR: δ = 2.30 (3H, s), 2.82 (1H, dd, J = 15.8, 8.7 Hz), 2.87 (1H, dd, J = 15.8, 7.2 Hz), 4.81 (1H, dd, J = 8.7, 7.2 Hz), 5.21 (1H, s), 5.66 (1H, s), 7.23–7.33 (5H, m); ^{13}C NMR: δ = 30.3, 35.7, 45.8, 120.9 (q, J_{CF} = 6 Hz), 123.4 (q, J_{CF} = 272 Hz), 127.7, 127.7, 128.7, 134.6 (q, J_{CF} = 30 Hz), 140.1, 194.0; ^{19}F NMR: δ_F = 93.4 (br s); elemental analysis: calcd (%) for $C_{13}H_{13}F_3OS$: C 56.92, H 4.78, found: C 56.89, H 4.90.

***S*-[2-(Trifluoromethyl)dec-1-en-4-yl] ethanethioate (8b):** To a solution of 2-(trifluoromethyl)dec-1-en-4-ol (**4d**) (540 mg, 2.41 mmol), PPh_3 (1.29 g, 4.90 mmol), and thioacetic acid (258 μL, 3.6 mmol) in THF (15 mL) was added DEAD (40% in toluene solution; 3.45 mL, 6.81 mmol) at –10 °C. The reaction mixture was stirred at 0 °C for 20 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane) to give **8b** (346 mg, 51%) as a pale yellow liquid. IR (neat): 2956, 2929, 2858, 1695, 1458, 1417, 1354, 1319, 1169, 1122, 951 cm^{-1}; ^1H NMR: δ = 0.87 (3H, t, J = 6.5 Hz), 1.27–1.75 (10H, m), 2.32 (3H, s), 2.47 (2H, d, J = 7.6 Hz), 3.66–3.73 (1H, m), 5.41 (1H, s), 5.78 (1H, s); ^{13}C NMR: δ = 14.0, 22.5, 26.6, 29.0, 30.7, 31.6, 34.2, 34.9, 42.4, 120.1 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 274 Hz), 135.4 (q, J_{CF} = 30 Hz), 195.2; ^{19}F NMR: δ_F = 93.3 (br s); HRMS (FAB): calcd for $C_{13}H_{22}F_3OS$ ([M + H] $^+$) 283.1343, found 283.1326.

Diethyl [1-phenyl-3-(trifluoromethyl)but-3-en-1-yl]malonate (10): To a mixture of trimethyl[2-(trifluoromethyl)prop-2-en-1-yl]silane (1.06g, 5.82 mmol), diethyl 2-benzylidenemalonate (**9**) (1.44g, 5.80 mmol) and molecular sieves 4Å (1.0 g) in THF (15 mL) was added a solution of tetrabutylammonium fluoride (TBAF, 1 M in THF; 0.69 mL, 0.69 mmol) at rt, and the mixture was stirred for 12 h at rt. The reaction was quenched with phosphate buffer (pH 7, 20 mL), and the solid materials were removed through Celite. After organic materials were extracted with EtOAc (10 mL × 3), the combined extracts were washed with water (10 mL × 2), brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (benzene) to give **10** (857 mg, 41%) as a colorless liquid. IR (neat): 3032, 2983, 2939, 2906, 1749, 1732, 1369, 1219, 1167, 1122 cm^{-1}; ^1H NMR: δ = 0.96 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.53 (1H, dd, J = 15.0, 10.1 Hz), 2.73 (1H, dd, J = 15.0, 3.2 Hz), 3.66 (1H, d, J = 10.1 Hz), 3.68 (1H, ddd, J = 10.1, 10.1, 3.2 Hz), 3.90 (2H, q, J = 7.1 Hz), 4.23 (1H, dq, J = 10.8, 7.2 Hz), 4.26 (1H, dq, J = 10.8, 7.2 Hz), 4.96 (1H, s), 5.51 (1H, s), 7.19 (2H, dd, J = 7.6, 7.6 Hz), 7.20 (1H, t, J = 7.6 Hz), 7.27 (2H, d, J = 7.6 Hz); ^{13}C NMR: δ = 13.6, 13.9, 33.8, 43.7, 58.4, 61.3, 61.7, 120.8 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 272 Hz), 127.2, 128.3, 128.5, 134.8 (q, J_{CF} = 30 Hz), 139.0, 167.4, 167.9; ^{19}F NMR: δ_F = 93.5 (br s); elemental analysis: calcd (%) for $C_{18}H_{21}F_3O_4$: C 60.33, H 5.91, found: C 60.26, H 6.01.

[1-Phenyl-3-(trifluoromethyl)but-3-en-1-yl]propanedinitrile (11): To a solution of 1-phenyl-3-(trifluoromethyl)but-3-en-1-ol (**4a**) (64 mg, 0.30 mmol), and malononitrile (28 mg, 0.43 mmol) in benzene (2 mL) was added Bu_3P=CHCN (107 mg, 0.44 mmol) at rt, and the reaction mixture was stirred at rt for 24 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **11** (23 mg, 29%) as a colorless liquid. IR (neat): 3070, 3035, 2908, 2260, 2192, 1456, 1348, 1169, 1120, 957 cm^{-1}; ^1H NMR: δ = 2.91 (1H, dd, J = 15.1, 8.8 Hz), 2.98 (1H, dd, J = 15.1, 7.0 Hz), 3.49–3.54 (1H, m), 3.99 (1H, d, J = 5.4 Hz), 5.35 (1H, s), 5.79 (1H, s), 7.35–7.45 (5H, m); ^{13}C NMR: δ = 29.3, 32.8, 44.2, 111.2, 111.3, 123.0 (q, J_{CF} = 6 Hz), 123.1 (q, J_{CF} = 272 Hz), 127.9, 129.4, 129.4, 133.4 (q, J_{CF} = 30 Hz), 135.1; ^{19}F NMR: δ_F = 94.1 (br s); elemental analysis: calcd (%) for $C_{14}H_{11}F_3N_2$: C 63.63, H 4.20, N 10.60, found: C 63.38, H 4.33, N 10.33.

Cyclization of 2 under aprotic conditions: To a suspension of NaH (60 % dispersion in mineral oil; 104 mg, 2.6 mmol) in DMF (3 mL) was added **2** (2 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was stirred for 5–7 h at 80 °C, and then phosphate buffer (pH 7, 20 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with water and brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 3-difluoromethylene-1-(4-methylbenzenesulfonyl)indoline (**12**).

3-Difluoromethylene-1-(4-methylbenzenesulfonyl)indoline (12a): Colorless crystals; yield 84%; IR (neat): 1760, 1597, 1475, 1464, 1362, 1269, 1169, 812, 752 cm^{-1}; ^1H NMR: δ = 2.37 (3H, s), 4.55 (2H, dd, J_{HF} = 4.1, 4.1 Hz), 7.03 (1H, dd, J = 7.5, 7.5 Hz), 7.22–7.27 (4H, m), 7.67–7.71 (3H, m); ^{13}C NMR: δ = 21.5, 49.2 (d, J_{CF} = 4 Hz), 88.2 (dd, J_{CF} = 22, 22 Hz), 114.8, 123.3 (d, J_{CF} = 2 Hz), 123.4 (d, J_{CF} = 2 Hz), 124.2, 127.2, 129.0, 129.9, 133.5, 142.7 (d, J_{CF} = 5 Hz), 144.6, 149.8 (dd. J_{CF} = 287, 287 Hz); ^{19}F NMR: δ_F = 74.9 (1F, dt, J_{FF} = 43 Hz, J_{FH} = 4 Hz), 77.8 (1F, dt, J_{FF} = 43 Hz, J_{FH} = 4 Hz); elemental analysis: calcd (%) for $C_{16}H_{13}F_2NO_2S$: C 59.80, H 4.08, N 4.36, found: C 59.96, H 4.25, N 4.18.

3-Difluoromethylene-5-methyl-1-(4-methylbenzenesulfonyl)indoline (12b): Colorless crystals; yield 72%; IR (neat): 2924, 1755, 1475, 1358, 1165, 912, 742 cm^{-1}; ^1H NMR: δ = 2.28 (3H, s), 2.36 (3H, s), 4.52 (2H, dd, J_{HF} = 4.3, 4.3 Hz), 7.04 (1H, d, J = 8.2 Hz), 7.06 (1H, s), 7.23 (2H, d, J = 8.3 Hz), 7.58 (1H, d, J = 8.2 Hz), 7.65 (2H, d, J = 8.3 Hz); ^{13}C NMR: δ = 20.9, 21.5, 49.4 (d, J_{CF} = 3 Hz), 88.3 (dd, J_{CF} = 22, 22 Hz), 114.7, 123.7 (d, J_{CF} = 9 Hz), 124.3 (dd, J_{CF} = 6, 4 Hz), 127.2, 129.7, 129.8, 133.5, 134.0, 140.5, 144.4, 149.6 (dd. J_{CF} = 288, 288 Hz); ^{19}F NMR: δ_F = 74.6 (1F, dt, J_{FF} = 43 Hz, J_{FH} = 4 Hz), 77.5 (1F, dt, J_{FF} = 43 Hz, J_{FH} = 4 Hz); elemental analysis: calcd (%) for $C_{17}H_{15}F_2NO_2S$: C 60.88, H 4.51, N 4.18, found: C 60.73, H 4.78, N 3.92.

6-Chloro-3-difluoromethylene-1-(4-methylbenzenesulfonyl)indoline (12c): Colorless crystals; yield 54%; IR (neat): 3020, 2927, 1757, 1597, 1475, 1363, 1215, 1167, 966 cm^{-1}; ^1H NMR: δ = 2.36 (3H, s), 4.52 (2H, dd, J_{HF} = 4.3, 4.3 Hz), 7.04 (1H, d, J = 8.2 Hz), 7.06 (1H, s), 7.23 (2H, d, J = 8.3 Hz), 7.58 (1H, d, J = 8.2 Hz), 7.65 (2H, d, J = 8.3 Hz); ^{13}C NMR: δ = 21.6, 49.6 (d, J_{CF} = 3 Hz), 87.6 (dd, J_{CF} = 27, 27 Hz), 114.9, 122.8 (dd, J_{CF} = 4, 4 Hz), 123.9 (dd, J_{CF} = 9, 2 Hz), 124.2, 127.2, 130.0, 133.3, 134.8, 143.6 (d, J_{CF} = 5 Hz), 144.9, 149.8 (dd. J_{CF} = 289, 289 Hz); ^{19}F NMR: δ_F = 75.7 (1F, dt, J_{FF} = 41 Hz, J_{FH} = 4 Hz), 78.4 (1F, dt, J_{FF} = 41 Hz, J_{FH} = 4 Hz); HRMS (FAB): calcd for $C_{16}H_{13}ClF_2NO_2S$ ([M + H]$^+$) 356.0324, found 356.0332.

Cyclization of 2 under protic conditions: To a solution of **2** (0.30 mmol) in DMF (3 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 mg, 0.010 mmol) at rt. After the mixture was stirred at 120 °C for 0.5–2 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 1-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)indoline (**13**).

1-(4-Methylbenzenesulfonyl)-3-(trifluoromethyl)indoline (13a): Colorless crystals; yield 81%; IR (neat): 2924, 1597, 1481, 1462, 1360, 1273, 1167, 1124, 1090, 814, 756, 660 cm^{-1}; ^1H NMR: δ = 2.37 (3H, s), 3.82–3.90 (1H, m), 4.05 (1H, dd, J = 11.8, 5.6 Hz), 4.11 (1H, dd, J = 11.8, 10.3 Hz), 7.05 (1H, dd, J = 7.8, 7.8 Hz), 7.24 (2H, d, J = 8.2 Hz), 7.25 (1H, d, J = 7.8 Hz), 7.34 (1H, dd, J = 7.8, 7.8 Hz), 7.68 (2H, d, J = 8.2 Hz), 7.70 (1H, d, J = 7.8 Hz); ^{13}C NMR: δ = 21.5, 44.3 (q, J_{CF} = 30 Hz), 49.2 (q, J_{CF} = 3 Hz), 114.9, 124.0, 124.3, 125.3 (q, J_{CF} = 279 Hz), 126.1, 127.2, 129.8, 130.2, 133.5, 142.9, 144.6; ^{19}F NMR: δ_F= 90.0 (d, J_{FH} = 9 Hz); elemental analysis: calcd (%) for $C_{16}H_{14}F_3NO_2S$: C 56.30, H 4.13, N 4.10, found: C 56.42, H 4.23, N 4.09.

5-Methyl-1-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)indoline (13b): Colorless crystals; yield 69%; IR (neat): 3022, 2924, 2362, 1599, 1489, 1358, 1217, 1167, 912, 771, 748 cm^{-1}; ^1H NMR: δ = 2.30 (3H, s), 2.37 (3H, s), 3.77–3.82 (1H, m), 4.02 (1H, dd, J = 11.5, 5.6 Hz), 4.07 (1H, dd, J = 11.5, 11.5 Hz), 7.05 (1H, s), 7.14 (1H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.59 (1H, d, J = 8.3 Hz), 7.66 (2H, d, J = 8.0 Hz); ^{13}C NMR: δ = 20.9, 21.5, 44.4 (q, J_{CF} = 30 Hz), 49.4 (q, J_{CF} = 3 Hz), 114.9, 124.5 (q, J_{CF} = 2 Hz), 125.4 (q, J_{CF} = 279 Hz), 126.5, 127.3, 129.8, 130.8, 133.4, 133.9, 140.6, 144.4; ^{19}F NMR: δ_F = 90.1 (d, J_{FH} = 9 Hz); HRMS (FAB): calcd for $C_{17}H_{17}F_3NO_2S$ ([M + H] $^+$) 356.0932, found 356.0947.

6-Chloro-1-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)indoline (13c): Colorless crystals; yield 71%; IR (neat): 2920, 1601, 1481, 1358, 1267, 1161, 1117, 1090, 1074 cm^{-1}; ^1H NMR: δ = 2.40 (3H, s), 3.78–3.87 (1H, m), 4.06 (1H, dd, J = 11.1, 5.1 Hz), 4.12 (1H, dd, J = 11.1, 9.8 Hz), 7.02 (1H, dd, J = 7.7, 1.9 Hz), 7.16 (1H, d, J = 7.7 Hz), 7.29 (2H, d, J = 7.6 Hz), 7.69 (2H, d, J = 7.6 Hz), 7.70 (1H, d, J = 1.9 Hz); ^{13}C NMR: δ = 21.6, 43.8 (q, J_{CF} = 30 Hz), 49.6 (q, J_{CF} = 3 Hz), 115.1, 124.1, 125.0 (q, J_{CF} = 279 Hz), 126.9, 127.2, 130.0, 133.2, 136.3, 144.0, 144.9, 149.8; ^{19}F NMR: δ_F = 89.7 (d, J_{FH} = 9 Hz); HRMS (FAB): calcd for $C_{16}H_{14}ClF_3NO_2S$ ([M + H] $^+$) 376.0386, found 376.0381.

1-(4-Methylbenzenesulfonyl)-3-trifluoromethyl-1*H*-indole (14): To a solution of **12a** (226 mg, 0.704 mmol) in CH_2Cl_2 (3 mL) was added $Et_3N{\cdot}3HF$ (285 mg, 1.77 mmol) and *N*-iodosuccinimide (364 mg, 1.62 mmol) at – 10 °C. After the reaction mixture was stirred at –10 °C for 2.5 h, aqueous $Na_2S_2O_3$ was added to quench the reaction. Organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **14** (214 mg, 90%) as colorless crystals. IR (neat): 3124, 3064, 2978, 1595, 1448, 1387, 1176, 1147, 1030, 912 cm^{-1}; ^1H NMR: δ = 2.37 (3H, s), 7.28 (2H, d, J = 8.5 Hz), 7.33 (1H, dd, J = 7.7, 7.7 Hz), 7.40 (1H, dd, J = 7.7, 7.7 Hz), 7.66 (1H, d, J = 7.7 Hz), 7.82 (2H, d, J = 8.5 Hz), 7.94 (1H, q, J_{HF} = 1.4 Hz), 7.99 (1H, d, J = 7.7 Hz); ^{13}C NMR: δ = 21.6, 112.9 (q, J_{CF} = 37 Hz), 113.6, 120.1, 122.8 (q, J_{CF} = 266 Hz), 124.2, 125.6, 125.9, 126.1 (q, J_{CF} = 6 Hz) 127.1, 130.2, 134.6, 134.7, 145.9; ^{19}F NMR: δ_F = 102.3 (br s); HRMS (FAB): calcd for $C_{16}H_{13}F_3NO_2S$ ([M + H] $^+$) 340.0619, found 340.0617.

3-Bromodifluoromethyl-1-(4-methylbenzenesulfonyl)-1*H*-indole (15): To a solution of **12a** (75 mg, 0.23 mmol) in CCl_4 (3 mL) was added Br_2 (52 mg, 0.32 mmol) in CCl_4 (0.3 mL) at rt. After the reaction mixture was stirred at rt for 2.5 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on Florisil (hexane–EtOAc, 5:1) to give **15** (89 mg, 96%) as colorless crystals. IR (neat): 3149, 3018, 2924, 1562, 1448, 1379, 1190, 1176, 958 cm^{-1}; ^1H NMR: δ = 2.38 (3H, s), 7.29 (2H, d, J = 8.6 Hz), 7.35 (1H, dd, J = 7.6, 7.6 Hz), 7.40 (1H, dd, J = 7.6, 7.6 Hz), 7.76 (1H, d, J = 7.6 Hz), 7.83 (2H, d, J = 8.6 Hz), 7.89 (1H, s), 7.97 (1H, d, J = 7.6 Hz); ^{13}C NMR: δ = 21.6, 113.5, 114.3 (t, J_{CF} = 297 Hz), 120.1 (t, J_{CF} = 28 Hz), 120.6, 124.1, 124.2 (t, J_{CF} = 7 Hz), 125.2 (t, J_{CF} = 3 Hz), 125.8, 127.1, 130.2, 134.5, 134.8, 145.8; ^{19}F NMR: δ_F = 121.9 (br s); elemental analysis: calcd (%) for $C_{16}H_{12}BrF_2NO_2S$: C 48.01, H 3.02, N 3.50, found: C 48.18, H 3.18, N 3.27.

3-Difluoromethyl-1-(4-methylbenzenesulfonyl)-1*H*-indole (16): To a solution of NaI (54 mg, 0.36 mmol) in CH_3CN (2 mL) was added Me_3SiCl (39 mg, 0.36 mmol), water (3.2 mg, 0.18 mmol), and then **12a** (72 mg, 0.23 mmol) at rt. The reaction mixture was stirred at rt for 10 h. The reaction was quenched with water (10 mL), and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **16** (69 mg, 96%) as colorless crystals. IR (neat): 3114, 3022, 2968, 1595, 1568, 1446, 1373, 1219, 1174 cm^{-1}; ^1H NMR: δ = 2.36 (3H, s), 6.86 (1H, t, J_{HF} = 55.6 Hz), 7.26 (2H, d, J = 8.4 Hz), 7.30 (1H, dd, J = 7.4, 7.4 Hz), 7.38 (1H, dd, J = 7.4, 7.4 Hz), 7.68 (1H, d, J = 7.4 Hz), 7.78 (1H, t, J_{HF} = 2.4 Hz), 7.80 (2H, d, J = 8.4 Hz), 7.98 (1H, d, J = 7.4 Hz); ^{13}C NMR: δ = 21.6, 111.8 (t, J_{CF} = 235 Hz), 113.7, 116.6 (t, J_{CF} = 26 Hz), 120.4, 123.9, 125.5 (t, J_{CF} = 10 Hz), 125.6, 126.6, 127.0, 130.1, 134.8, 135.0, 145.6; ^{19}F NMR: δ_F = 50.6 (dd, J_{FH} = 56, 2 Hz); elemental analysis: calcd (%) for $C_{16}H_{13}F_2NO_2S$: C 59.80, H 4.08, N 4.36, found: C 59.83, H 4.18, N 4.14.

3-Difluoromethylene-2,3-dihydro-1-benzothiophene (17): To a solution of **3** (106 mg, 0.432 mmol) in THF (3 mL) was added potassium butoxide (KO*t*-Bu, 53 mg, 0.48 mmol) at 0 °C. The reaction mixture was heated under reflux for 2 h, and then phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane) to give **17** (52 mg, 65%) as a colorless liquid. IR (neat): 3018, 1732, 1464, 1446, 1327, 1252, 1217, 1105, 982, 906 cm^{-1}; ^1H NMR: δ = 4.04 (2H, dd, J_{HF} = 4.1, 4.1 Hz), 7.06 (1H, ddd, J = 7.7, 7.7, 1.3 Hz), 7.13 (1H, ddd, J = 7.7, 7.7, 1.3 Hz), 7.16 (1H, dd, J = 7.7, 1.3 Hz), 7.38 (1H, dd, J = 7.7,

1.3 Hz); ^{13}C NMR: δ = 30.1 (d, J_{CF} = 3 Hz), 94.2 (dd, J_{CF} = 26, 26 Hz), 122.1, 124.0 (dd, J_{CF} = 2, 2 Hz), 124.6, 128.3 (dd, J_{CF} = 3, 3 Hz), 131.5 (dd, J_{CF} = 3, 3 Hz), 142.7 (d, J_{CF} = 5 Hz), 152.0 (dd. J_{CF} = 288, 288 Hz); ^{19}F NMR: δ_F = 75.6 (1F, dt, J_{FF} = 40 Hz, J_{FH} = 5 Hz), 78.4 (1F, dt, J_{FF} = 40 Hz, J_{FH} = 5 Hz); elemental analysis: calcd (%) for $C_9H_6F_2S$: C 58.68, H 3.28, found: C 58.46, H 3.50.

3-Trifluoromethyl-2,3-dihydro-1-benzothiophene (18): To a solution of **3** (97 mg, 0.39 mmol) in MeOH (3 mL) was added K_2CO_3 (52 mg, 0.378 mmol) at rt. After the mixture was heated under reflux for 1 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane) to give **18** (49 mg, 61%) as a colorless liquid. IR (neat): 3018, 1587, 1466, 1446, 1350, 1265, 1215, 1159, 1107 cm^{-1}; ^{1}H NMR: δ = 3.49 (1H, dd, J = 12.0, 6.6 Hz), 3.59 (1H, dd, J = 12.0, 9.0 Hz), 4.12–4.20 (1H, m), 7.08 (1H, dd, J = 7.6, 7.6 Hz), 7.21–7.25 (2H, m), 7.34 (1H, d, J = 7.6 Hz); ^{13}C NMR: δ = 31.4 (q, J_{CF} = 3 Hz), 51.5 (q, J_{CF} = 28 Hz), 122.5, 124.6, 126.0, 126.2 (q, J_{CF} = 280 Hz), 129.5, 132.6, 142.7; ^{19}F NMR: δ_F = 91.2 (d, J_{FH} = 9 Hz); HRMS (FAB): calcd for $C_9H_8F_3S$ ([M + H]$^+$) 205.0299, found 205.0295.

Cyclization of 5 under aprotic conditions: To a solution of **5** (1.0 mmol) in DMF (10 mL) was added NaH (60% dispersion in mineral oil; 52 mg, 1.3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then 120 °C for 0.5–4 h. Phosphate buffer (pH 7, 20 mL) was added to quench the reaction, and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 3-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine (**19**).

4-Difluoromethylene-1-(4-methylbenzenesulfonyl)-2-phenylpyrrolidine (19a): Colorless crystals; yield 91%; IR (neat): 3064, 3032, 2927, 2866, 1782, 1350, 1273, 1219, 1161, 1093, 1058 cm^{-1}; ^{1}H NMR: δ = 2.42 (3H, s), 2.54 (1H, br d, J = 15.0 Hz), 2.66–2.74 (1H, m), 4.13 (1H, dm, J = 14.5 Hz), 4.19 (1H, dm, J = 14.5 Hz), 4.95 (1H, ddd, J = 8.2, 3.1, 1.5 Hz), 7.22– 7.31 (7H, m), 7.57 (2H, d, J = 8.3 Hz); ^{13}C NMR: δ = 21.5, 33.9, 47.0 (d, J_{CF} = 4 Hz), 63.2, 85.4 (dd, J_{CF} = 25, 22 Hz), 126.2, 127.4, 127.7, 128.5, 129.6, 134.8, 140.8, 143.7, 149.8 (dd, J_{CF} = 283, 283 Hz); ^{19}F NMR: δ_F = 72.0 (1F, dm, J_{FF} = 54 Hz), 74.5 (1F, d, J_{FF} = 54 Hz); elemental analysis: calcd (%) for $C_{18}H_{17}F_2NO_2S$: C 61.88, H 4.90, N 4.01, found: C 61.81, H 4.95, N 3.74.

2-(4-Bromophenyl)-4-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine (19b): Colorless crystals; yield 79%; m.p. 76–77 °C; IR (neat): 3026, 1782, 1489, 1350, 1275, 1219, 1163 cm^{-1}; ^{1}H NMR: δ = 2.43 (3H, s), 2.49 (1H, br d, J = 15.0 Hz), 2.67–2.74 (1H, m), 4.13 (1H, br d, J = 15.0 Hz), 4.16 (1H, br d, J = 15.0 Hz), 4.86 (1H, dm, J = 7.9 Hz), 7.11 (2H, d, J = 8.4 Hz), 7.26 (2H, d, J = 7.8 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 7.8 Hz); ^{13}C NMR: δ = 21.5, 33.9, 47.0 (d, J_{CF} = 4 Hz), 62.6, 85.1 (dd, J_{CF} = 26, 24 Hz), 121.6, 127.3, 128.0, 129.7, 131.6, 134.6, 139.9, 143.9, 149.9 (dd, J_{CF} = 285, 285 Hz); ^{19}F NMR: δ_F = 72.4 (1F, ddd, J_{FF} = 53 Hz, J_{FH} = 3, 3 Hz), 74.9 (1F, d, J_{FF} = 53 Hz); elemental analysis: calcd (%) for $C_{18}H_{16}BrF_2NO_2S$: C 50.48, H 3.77; N 3.27, found: C 50.49, H 3.93, N 3.15.

4-Difluoromethylene-2-(2-furyl)-1-(4-methylbenzenesulfonyl)pyrrolidine (19c): Colorless crystals; yield 74%; m.p. 63–64 °C; IR (neat): 3120, 3028, 2924, 2868, 1784, 1599, 1350, 1275, 1163, 1093 cm^{-1}; ^{1}H NMR: δ = 2.40 (3H, s), 2.64–2.68 (2H, m), 3.99 (1H, dm, J = 13.4 Hz), 4.18 (1H, dm, J = 13.4 Hz), 5.09 (1H, ddd, J = 6.3, 4.1, 1.9 Hz), 6.24 (1H, br d, J = 3.3 Hz), 6.25 (1H, dd, J = 3.3, 1.9 Hz), 7.18–7.19 (1H, m), 7.23 (2H, d, J = 8.3 Hz), 7.54 (2H, d, J = 8.3 Hz); ^{13}C NMR: δ = 21.5, 30.9 (dd, J_{CF} = 2, 2 Hz), 46.2 (dd, J_{CF} = 4, 1 Hz), 55.6, 85.6 (dd, J_{CF} = 26, 23 Hz), 107.6, 110.1, 127.2, 129.6, 134.8, 142.3, 143.5, 149.9 (dd, J_{CF} = 282, 282 Hz), 152.6; ^{19}F NMR: δ_F = 71.8 (1F, ddd, J_{FF} = 55, J_{FH} = 3, 3 Hz), 74.4 (1F, d, J_{FF} = 55 Hz); elemental analysis: calcd (%) for $C_{16}H_{15}F_2NO_3S$: C 56.63, H 4.46, N 4.13, found: C 56.45, H 4.45, N 3.86.

4-Difluoromethylene-2-hexyl-1-(4-methylbenzenesulfonyl)pyrrolidine (19d): A colorless liquid; yield 82%; IR (neat): 3026, 2956, 2927, 2858, 1782, 1348, 1217, 1163, 912 cm^{-1}; ^{1}H NMR: δ = 0.89 (3H, t, J = 6.5 Hz), 1.21–1.46 (10H, m), 2.06–2.16 (2H, m), 2.43 (3H, s), 3.83–3.90 (1H, m), 3.96 (1H, dm, J = 14.7 Hz), 4.03 (1H, dm, J = 14.7 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.70 (2H, d, J = 8.4 Hz); ^{13}C NMR: δ = 14.1, 21.5, 22.6, 25.7, 29.0, 30.2, 31.7, 35.4, 46.2 (d, J_{CF} = 3 Hz), 60.7, 85.9 (dd, J_{CF} = 25, 22 Hz), 127.3, 129.8, 135.1, 143.7, 149.9 (dd, J_{CF} = 282, 282 Hz); ^{19}F NMR: δ_F = 71.4 (1F, ddd, J_{FF} = 56, J_{FH} = 3, 3 Hz), 74.2 (1F, d, J_{FF} = 56 Hz); elemental analysis: calcd (%) for $C_{18}H_{25}F_2NO_2S$: C 60.48, H 7.05, N 3.92, found: C 60.50, H 7.10, N 3.63.

3-Difluoromethylene-1-(4-methylbenzenesulfonyl)-4-phenylpyrrolidine (19e): Colorless crystals; yield 65%; IR (neat): 3030, 2924, 1774, 1597, 1495, 1350, 1271, 1163, 1093 cm^{-1}; ^{1}H NMR: δ = 2.45 (3H, s), 3.36 (1H, ddd, J = 9.5, 4.7, 1.4 Hz), 3.61 (1H, dd, J = 9.5, 7.7 Hz), 3,94–3.98 (2H, m), 4.02 (1H, dddd, J = 13.2, 3.7, 1.4 Hz, J_{HF} = 3.7 Hz), 7.15 (2H, d, J = 6.8 Hz), 7.22–7.29 (3H, m), 7.34 (2H, d, J = 8.1 Hz), 7.71 (2H, d, J = 8.1 Hz); ^{13}C NMR: δ = 21.5, 43.2, 47.2 (d, J_{CF} = 4 Hz), 56.2, 90.3 (dd, J_{CF} = 23, 21 Hz), 126.9, 127.3, 127.9, 128.8, 129.8, 132.0, 139.9, 144.1, 150.8 (dd, J_{CF} = 288, 288 Hz); ^{19}F NMR: δ_F = 73.96 (1F, ddd, J_{FF} = 48 Hz, J_{FH} = 3, 3 Hz), 76.1 (1F, d, J_{FF} = 48 Hz); elemental analysis: calcd (%) for $C_{18}H_{17}F_2NO_2S$: C 61.88, H 4.90, N 4.01, found: C 62.05, H 5.01, N 3.89.

3-Difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine (19f): Colorless crystals; yield 83%; IR (neat): 2924, 2864, 1782, 1348, 1269, 1161, 1093, 1072, 1039, 812 cm^{-1}; ^{1}H NMR: δ = 2.45 (3H, s), 2.44–2.48 (2H, m), 3.30 (2H, ddd, J = 7.0, 7.0, 1.3 Hz), 3.79–3.82 (2H, m), 7.36 (2H, d, J = 8.1 Hz), 7.72 (2H, d, J = 8.1 Hz); ^{13}C NMR: δ = 21.5, 24.6, 46.5 (d, J_{CF} = 4 Hz), 48.0, 85.8 (dd, J_{CF} = 27, 22 Hz), 127.8, 129.8, 132.3, 144.0, 149.9 (dd, J_{CF} = 285, 285 Hz); ^{19}F NMR: δ_F = 71.6 (1F, dm, J_{FF} = 55 Hz), 74.0 (1F, d, J_{FF} = 55 Hz); elemental analysis: calcd (%) for $C_{12}H_{13}F_2NO_2S$: C 52.74, H 4.79, N 5.13, found: C 52.83, H 4.88, N 4.87.

Cyclization of 5 under protic conditions: To a solution of **5** (0.3 mmol) in ethane-1,2-diol (3 mL) was added KOH powder (84 mg, 1.5 mmol) at rt. After the reaction mixture was stirred at 130 °C for 10–20 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (20 mL × 3), and the combined extracts were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 3-trifluoromethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (**20**) as a mixture of *trans*- and *cis*-isomers.

1-(4-Methylbenzenesulfonyl)-2-phenyl-4-(trifluoromethyl)pyrrolidine (20a): Colorless crystals; yield 85% (*trans*:*cis* = 92:8); m.p. 90–91 °C; IR (neat): 3030, 2983, 2881, 1452, 1400, 1348, 1157, 1120 cm^{-1}; ^{1}H NMR: ***trans*** δ = 2.05 (2H, dd, J = 8.6, 5.4 Hz), 2.44 (3H, s), 2.88–3.06 (1H, m), 3.50 (1H, dd, J = 10.5, 8.8 Hz), 3.85 (1H, dd, J = 10.5, 8.3 Hz), 4.94 (1H, dd, J = 5.4, 5.4 Hz), 7.23–7.48 (7H, m), 7.67 (2H, d, J = 8.2 Hz); ***cis*** δ = 2.42 (3H, s), 2.48–2.53 (2H, m), 2.58–3.68 (1H, m), 3.58 (1H, dd, J = 11.5, 9.8 Hz), 3.96 (1H, dd, J = 11.5, 8.1 Hz), 4.71 (1H, dd, J = 9.3, 7.3 Hz), 7.23–7.48 (7H, m), 7.54 (2H, d, J = 8.2 Hz); ^{13}C NMR: ***trans*** δ = 21.6, 34.8, 40.9 (q, J_{CF} = 29 Hz), 47.7, 62.6, 125.9, 126.1 (q, J_{CF} = 275 Hz), 127.5, 127.7, 128.6, 129.7, 134.2, 141.1, 143.9; ^{19}F NMR: ***trans*** δ_F = 91.1 (d, J_{FH} = 8 Hz,); ***cis*** δ_F = 91.3 (d, J_{FH} = 8 Hz); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79, found: C 58.43, H 5.00, N 3.59.

2-(4-Bromophenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (20b): Separation of *cis*- and *trans*-isomer was achieved by column chromatography (hexane–EtOAc, 5:1) to give ***trans*-20b** (70%) and ***cis*-20b** (6%) as colorless crystals. **(*trans*-20b)** m.p. 119–120 °C; IR (neat): 3030, 2910, 1489, 1400, 1350, 1163, 1122, 914 cm^{-1}; ^{1}H NMR: δ = 2.01 (1H, ddd, J = 12.9, 7.2, 3.3 Hz), 2.08 (1H, ddd, J = 12.9, 9.9, 8.2 Hz), 2.45 (3H, s), 2.86–2.99 (1H, m), 3.47 (1H, dd, J = 10.6, 8.6 Hz), 3.85 (1H, dd, J = 10.6, 8.2 Hz), 4.83 (1H, dd, J = 8.2, 3.3 Hz), 7.17 (2H, d, J = 8.5 Hz), 7.33 (2H, d, J = 8.1 Hz), 7.45 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.1 Hz); ^{13}C NMR: δ = 21.6, 34.8 (q, J_{CF} = 2 Hz), 40.8 (q, J_{CF} = 29 Hz), 47.8 (q, J_{CF} = 3 Hz), 62.1, 121.6, 126.0 (q, J_{CF} = 276 Hz), 127.5, 127.7, 129.8, 131.7, 134.0, 140.2, 144.1; ^{19}F NMR: δ_F = 91.1 (d, J_{FH} = 8 Hz); elemental analysis: calcd (%) for $C_{18}H_{17}BrF_3NO_2S$: C 48.23, H 3.82, N 3.12, found: C 48.04, H 3.84, N 2.87; **(*cis*-20b)** IR (neat): 2960, 2910, 1489, 1404, 1360, 1271, 1161, 912 cm^{-1}; ^{1}H NMR: δ = 1.99 (1H, ddd, J = 13.3, 11.0, 9.4 Hz), 2.44 (3H, s), 2.52 (1H, ddd, J = 13.3, 7.5, 7.5 Hz), 2.58–2.71 (1H, m), 3.58 (1H, dd, J = 11.5, 9.7 Hz), 3.94 (1H, dd, J = 11.5, 8.2 Hz), 4.65 (1H, dd, J = 9.4, 7.5 Hz), 7.14 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.54 (2H, d, J = 8.0 Hz); ^{13}C NMR: δ = 21.6, 36.2, 41.6 (q, J_{CF} = 30 Hz), 48.5 (q, J_{CF} = 3 Hz), 63.0, 121.7, 125.6 (q, J_{CF} = 276 Hz), 127.4, 128.2, 129.8, 131.6, 134.6, 139.7, 144.1; ^{19}F NMR: δ_F = 91.2 (d, J_{FH} = 8 Hz); elemental analysis: calcd (%) for $C_{18}H_{17}BrF_3NO_2S$: C 48.23, H 3.82, N 3.12, found: C 48.30, H 3.90, N 2.90.

2-(2-Furyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (20c): A colorless liquid; yield 69% (*trans*:*cis* = 83:17); IR (neat): 2958, 2925, 1599, 1348, 1271, 1159, 1120, 1011, 912 cm^{-1}; ^{1}H NMR: ***trans*** δ = 2.10 (1H, ddd, J = 12.6, 10.8, 8.2 Hz), 2.20 (1H, ddd, J = 12.6, 7.2, 1.9 Hz), 2.41 (3H, s), 3.20–3.33 (1H, m), 3.52 (1H, dd, J = 10.0, 8.4 Hz), 3.67 (1H, dd, J = 10.0, 8.8 Hz), 5.05 (1H, br d, J = 8.2 Hz), 6.28 (1H, dd, J = 3.2, 1.9 Hz), 6.30 (1H, dm, J = 3.2 Hz), 7.20 (1H, dd, J = 1.9, 0.9 Hz), 7.26 (2H, d, J = 8.3 Hz), 7.53 (2H, d, J = 8.3 Hz); ***cis*** δ = 2.26–2.33 (1H, m), 2.41 (3H, s), 2.43–2.48 (1H, m), 2.72–2.82 (1H, m), 3.45 (1H, dd, J = 10.5, 10.5 Hz), 3.94 (1H, dd, J = 10.5, 7.9 Hz), 4.96 (1H, dd, J = 8.0, 8.0 Hz), 6.27 (1H, dd, J = 3.2, 1.8 Hz), 6.31 (1H, dm, J = 3.2 Hz), 7.20–7.22 (1H, m), 7.26 (2H, d, J = 8.3 Hz), 7.50 (2H, d, J = 8.3 Hz); ^{13}C NMR: ***trans*** δ = 21.5, 31.5 (q, J_{CF} = 2 Hz), 41.7 (q, J_{CF} = 29 Hz), 46.7 (q, J_{CF} = 3 Hz), 56.2, 108.1, 110.2, 126.2 (q, J_{CF} = 275 Hz), 127.2, 129.6, 134.6, 142.2, 143.6, 152.9; ^{19}F NMR: ***trans*** δ_F = 90.9 (d, J_{FH} = 8 Hz); ***cis*** δ_F = 91.5 (d, J_{FH} = 8 Hz); elemental analysis: calcd (%) for $C_{16}H_{16}F_3NO_3S$: C 53.48, H 4.49, N 3.90, found: C 53.52, H 4.65, N 3.72.

2-Hexyl-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (20d): Solvent (ethane-1,2-diol:THF, 10:1) was used. A colorless liquid; yield 67% (*trans*:*cis* = 77:23); IR (neat): 2956, 2929, 2858, 1456, 1402, 1348, 1273, 1163, 914 cm^{-1}; ^{1}H NMR: ***trans*** δ = 0.89 (3H, t, J = 7.0 Hz), 1.25–1.53 (9H, m), 1.60–1.68 (1H, m), 1.75–1.83 (2H, m), 2.44 (3H, s), 2.89–3.02 (1H, m), 3.24 (1H, dd, J = 10.5, 9.1 Hz), 3.65 (1H, dd, J = 10.5, 8.3 Hz), 3.70–3.78 (1H, m), 7.33 (2H, d, J = 8.0 Hz), 7.71 (2H, d, J = 8.0 Hz); ***cis*** δ = 0.89 (3H, t, J = 7.0 Hz), 1.25–1.53 (9H, m), 1.60–1.68 (1H, m), 1.87–1.94 (1H, m), 2.12 (1H, ddd, J = 12.8, 8.1, 8.1 Hz), 2.21–2.33 (1H, m), 2.45 (3H, s), 3.31 (1H, dd, J = 10.5, 8.8 Hz), 3.70–3.78 (2H, m), 7.34 (2H, d, J = 8.0 Hz), 7.72 (2H, d, J = 8.0 Hz); ^{13}C NMR: ***trans*** δ = 14.0, 21.4, 22.5, 25.8, 29.0, 30.0, 31.7, 35.8, 41.1 (q, J_{CF} = 29 Hz), 47.2 (q, J_{CF} = 2 Hz), 60.1, 126.2 (q, J_{CF} = 276 Hz), 127.4, 129.7, 134.0, 143.7; ^{19}F NMR: ***trans*** δ_F = 90.9 (d, J_{FH} = 8 Hz); ***cis*** δ_F = 91.5 (d, J_{FH} = 8 Hz); elemental analysis: calcd (%) for $C_{18}H_{26}F_3NO_2S$: C 57.27, H 6.94, N 3.71, found: C 57.32, H 6.99, N 3.53.

1-(4-Methylbenzenesulfonyl)- 3-phenyl-4-(trifluoromethyl)pyrrolidine (20e): Yield 57% (*trans*:*cis* = 72:28); **(*trans*-20e)** colorless crystals; m.p. 84–86 °C; IR (neat): 3032, 2956, 1599, 1348, 1265, 1163, 1113, 1028, 663 cm^{-1}; ^{1}H NMR: δ = 2.48 (3H, s), 2.96 (1H, dddq, J = 8.4, 8.4, 8.4 Hz, J_{HF} = 8.4 Hz), 3.33–3.43 (3H, m), 3.64 (1H, dd, J = 9.3, 8.4 Hz), 3.70 (1H, dd, J = 10.7, 8.8 Hz), 7.16 (2H, d, J = 7.7 Hz), 7.24–7.33 (3H, m), 7.38 (2H, d, J = 7.9 Hz), 7.74 (2H, d, J = 7.9 Hz); ^{13}C NMR: δ = 21.6, 44.3, 47.4 (q, J_{CF} = 3 Hz), 49.5 (q, J_{CF} = 28 Hz), 54.8, 126.1 (q, J_{CF} = 279 Hz), 127.0, 127.7, 127.8, 129.0, 129.9, 132.5, 139.2, 144.2; ^{19}F NMR: δ_F = 91.4 (d, J_{FH} = 9 Hz); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79, found: C 58.82, H 5.19, N 3.73; **(*cis*-20e)** colorless crystals; m.p. 96–97 °C; IR (neat): 3032, 2960, 1599, 1400, 1348, 1281, 1163, 1120, 1049 cm^{-1}; ^{1}H NMR: δ = 2.48 (3H, s), 3.00 (1H, dddq, J = 8.5, 8.5, 8.5 Hz, J_{HF} = 8.5 Hz), 3.56–3.75 (5H, m), 7.08–7.10 (2H, m), 7.24–7.26 (3H, m), 7.40 (2H, d, J = 8.0 Hz), 7.79 (2H, d, J = 8.0 Hz); ^{13}C NMR: δ = 21.6, 43.9, 46.4 (q, J_{CF} = 3 Hz), 46.9 (q, J_{CF} = 27 Hz), 52.5, 125.3 (q, J_{CF} = 280 Hz), 127.5, 127.7, 128.1, 128.5, 130.0, 133.5, 136.2, 144.1; ^{19}F NMR: δ_F = 96.5 (d, J_{HF} = 9 Hz); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79, found: C 58.70, H 5.04, N 3.73.

Cyclization of 7: To a solution of **7** (0.14 mmol) in THF (2 mL) was added KO*t*-Bu (20.4 mg, 0.18 mmol) at rt. The reaction mixture was heated to reflux for 2.5–6 h, and then phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (hexane–EtOAc, 10:1) to give 3-difluoromethylene-2,3,4,5-tetrahydrofuran (**21**).

4-Difluoromethylene-3,3-dimethyl-2-phenyl-2,3,4,5-tetrahydrofuran (21a): A colorless liquid; yield 80%; IR (neat): 3032, 2970, 2931, 2850, 1766, 1466, 1271, 1226, 1030, 723, 700 cm^{-1}; ^{1}H NMR: δ = 0.74 (3H, s), 1.31 (3H, s), 4.42 (1H, ddd, J = 12.3 Hz, J_{HF} = 4.7, 4.1 Hz), 4.52 (1H, s), 4.67 (1H, ddd, J = 12.3 Hz, J_{HF} = 2.8, 2.8 Hz), 7.30–7.36 (5H, m); ^{13}C NMR: δ = 21.9, 22.6, 43.7 (dd, J_{CF} = 4, 3 Hz), 65.0 (d, J_{CF} = 4

Hz), 90.6, 97.9 (dd, J_{CF} = 18, 18 Hz), 126.7, 127.8, 127.9, 136.8, 149.2 (dd, J_{CF} = 287, 284 Hz); ^{19}F NMR: δ_F = 67.6 (1F, d, J_{FF} = 66 Hz), 75.4 (1F, d, J_{FF} = 66 Hz); HRMS (FAB): calcd for $C_{13}H_{15}F_2O$ ([M + H]$^+$) 225.1091, found 225.1107.

4-Difluoromethylene-1-phenyl-2-oxaspiro[4.4]nonane (21b): A colorless liquid; yield 70%; IR (neat): 3032, 2956, 2870, 1765, 1454, 1265, 1217, 1051, 985, 729, 702 cm^{-1}; ^{1}H NMR: δ = 0.76–0.81 (1H, m), 1.40–1.50 (3H, m), 1.59–1.67 (2H, m), 1.86 (1H, ddd, J = 13.6, 8.3, 8.3 Hz), 2.09 (1H, ddd, J = 13.6, 8.8, 6.7 Hz), 4.46 (1H, ddd, J = 12.1 Hz, J_{HF} = 4.1, 3.5 Hz), 4.65 (1H, ddd, J = 12.1 Hz, J_{HF} = 2.9, 2.9 Hz), 4.66 (1H, s), 7.29–7.36 (5H, m); ^{13}C NMR: δ = 24.9, 25.6, 34.2 (d, J_{CF} = 2 Hz), 34.3, 54.3 (d, J_{CF} = 4 Hz), 65.6 (d, J_{CF} = 4 Hz), 90.1, 99.1 (dd, J_{CF} = 19, 17 Hz), 127.3, 127.9, 127.9, 137.4, 148.9 (dd, J_{CF} = 286, 283 Hz); ^{19}F NMR: δ_F = 68.2 (1F, d, J_{FF} = 65 Hz), 74.7 (1F, dd, J_{FF} = 65 Hz, J_{FH} = 4 Hz); HRMS (FAB): calcd for $C_{15}H_{17}F_2O$ ([M + H]$^+$) 251.1247, found 251.1271.

4-Difluoromethylene-3,3-dimethyl-2-(2-phenylethyl)-2,3,4,5-tetrahydrofuran (21c): A colorless liquid; yield 87%; IR (neat): 3028, 2956, 2927, 2854, 1768, 1496, 1456, 1277, 1227, 1027, 698 cm^{-1}; ^{1}H NMR: δ = 1.02 (3H, s), 1.17 (3H, s), 1.63–1.81 (2H, m), 2.63 (1H, ddd, J = 13.6, 10.0, 6.8 Hz), 2.91 (1H, ddd, J = 13.6, 10.4, 5.2 Hz), 3.42 (1H, dd, J = 10.0, 2.4 Hz), 4.25 (1H, ddd, J = 12.4 Hz, J_{HF} = 4.4, 4.0 Hz), 4.47 (1H, ddd, J = 12.4 Hz, J_{HF} = 2.8, 2.8 Hz), 7.17–7.31 (5H, m); ^{13}C NMR: δ = 20.8, 22.7 (d, J_{CF} = 4 Hz), 30.8, 33.3, 42.5 (d, J_{CF} = 3 Hz), 64.9 (d, J_{CF} = 4 Hz), 88.3, 98.3 (dd, J_{CF} = 18, 18 Hz), 125.9, 128.4, 128.4, 142.0, 149.1 (dd, J_{CF} = 286, 283 Hz); ^{19}F NMR: δ_F = 67.3 (1F, d, J_{FF} = 66 Hz), 75.1 (1F, d, J_{FF} = 66 Hz); HRMS (FAB): calcd for $C_{15}H_{19}F_2O$ ([M + H]$^+$) 253.1404, found 253.1384.

4-Difluoromethylene-2-phenyl-2,3,4,5-tetrahydrothiophene (22a): To a solution of **8a** (80 mg, 0.29 mmol) in DMF (3 mL) was added NaOMe (19 mg, 0.36 mmol) at 0 °C. After the reaction mixture was stirred at 100 °C for 10 h, phosphate buffer (pH 7, 20 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **22a** (51 mg, 82%) as a colorless liquid. IR (neat): 3064, 3030, 2912, 1765, 1267, 1219, 1049 cm^{-1}; ^{1}H NMR: δ = 2.72–2.78 (1H, m), 3.06 (1H, dd, J = 13.7, 5.7 Hz), 3.63 (1H, d, J = 13.6 Hz), 3.69 (1H, d, J = 13.6 Hz), 4.52 (1H, dd, J = 8.4, 5.7 Hz), 7.26 (1H, t, J = 7.3Hz), 7.33 (2H, dd, J = 7.3, 7.3 Hz), 7.38 (2H, d, J = 7.3 Hz); ^{13}C NMR: δ = 30.2 (d, J_{CF} = 2 Hz), 38.5 (d, J_{CF} = 2 Hz), 51.8, 90.0 (dd, J_{CF} = 22, 22 Hz), 127.3, 127.6, 128.6, 140.6, 150.3 (dd, J_{CF} = 284, 284 Hz); ^{19}F NMR: δ_F = 71.7 (1F, ddd, J_{FF} = 54 Hz, J_{FH} = 3, 3 Hz), 72.6 (1F, dd, J_{FF} = 54 Hz, J_{FH} = 4 Hz); HRMS (FAB): calcd for $C_{11}H_{11}F_2S$ ([M + H]$^+$) 213.0550, found 213.0564.

4-Difluoromethylene-2-hexyl-2,3,4,5-tetrahydrothiophene (22b): Compound **22b** was prepared by the method described for **22a** using **8b** (80 mg, 0.28 mmol), NaOMe (20 mg, 0.37 mmol) in DMF (3 mL) at 100 °C for 15 h. Purification by column chromatography (hexane–EtOAc, 50:1) gave **22b** (47 mg, 75%) as a colorless liquid. IR (neat): 2956, 2926, 2854, 1765, 1267, 1201, 1047, 912 cm^{-1}; ^{1}H NMR: δ = 0.88 (3H, t, J = 7.1 Hz), 1.22–1.41 (8H, m), 1.50–1.59 (1H, m), 1.60–1.68 (1H, m), 2.27–2.34 (1H, m), 2.78 (1H, dm, J = 14.3 Hz), 3.31–3.37 (1H, m), 3.45 (1H, dm, J = 12.9 Hz), 3.48 (1H, dm, J = 12.9 Hz); ^{13}C NMR: δ = 14.0, 22.6, 28.6, 28.8 (d, J_{CF} = 1 Hz), 29.1, 31.7, 36.1, 36.4 (dd, J_{CF} = 2, 2 Hz), 48.8, 89.8 (dd, J_{CF} = 21, 21 Hz), 150.4 (dd, J_{CF} = 283, 283 Hz); ^{19}F NMR: δ_F = 70.6 (1F, dm, J_{FF} = 56 Hz), 72.2 (1F, d, J_{FF} = 56 Hz); elemental analysis: calcd (%) for $C_{11}H_{18}F_2S$: C 59.97, H 8.23, found: C 59.84, H 8.21.

2-Phenyl-4-trifluoromethyl-2,3,4,5-tetrahydrothiophene (23a): To a solution of **8a** (87 mg, 0.32 mmol) in MeOH (3 mL) was added K_2CO_3 (47 mg, 0.34 mmol) at rt. After the reaction mixture was heated at reflux for 2 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **23a** (>98:2 mixture, 66 mg, 90%) as a colorless liquid. IR (neat): 3064, 3020, 2945, 2875, 1381, 1267, 1215, 1151, 1107 cm^{-1}; ^{1}H NMR: δ = 2.35 (1H, ddd, J = 13.3, 6.2, 6.2 Hz), 2.53 (1H, ddd, J = 13.3, 8.0, 7.1 Hz), 3.05–3.15 (2H, m), 3.23–3.30 (1H, m), 4.64 (1H, dd, J = 7.1, 6.2 Hz), 7.26 (1H, t, J = 7.4 Hz), 7.34 (2H, dd, J = 7.4, 7.4 Hz), 7.41 (2H, d, J = 7.4 Hz); ^{13}C NMR: δ = 31.2 (q, J_{CF} = 2 Hz), 39.4 (q, J_{CF} = 1 Hz), 46.0 (q, J_{CF} = 27 Hz), 50.8, 127.0 (q, J_{CF} = 277 Hz), 127.4, 127.4, 128.6, 141.6; ^{19}F NMR: δ_F = 91.8 (d, J_{FH} = 8 Hz); HRMS (FAB): calcd for $C_{11}H_{12}F_3S$ ([M + H]$^+$) 233.0612, found 233.0625.

2-Hexyl-4-trifluoromethyl-2,3,4,5-tetrahydrothiophene (23b): Compound **23b** was prepared by the method described for **23a** using **8b** (81 mg, 0.29 mmol) and K_2CO_3 (43 mg, 0.31 mmol) in MeOH (3 mL) for 1 h. Purification by column chromatography (hexane–EtOAc, 50:1) gave **23b** (92:8 mixture, 56 mg, 82%) as a colorless liquid. IR (neat): 2956, 2927, 2873, 2856, 1380, 1269, 1161, 1111 cm^{-1}; ^{1}H NMR: δ = 0.88 (3H, t, J = 7.1 Hz), 1.23–1.65 (10H, m), 1.98–2.03 (1H, m), 2.19 (1H, ddd, J = 12.9, 8.4, 7.0 Hz), 2.91–3.05 (3H, m), 3.37–3.43 (1H, m); ^{13}C NMR: δ = 14.0, 22.5, 28.4, 29.0, 30.2 (q, J_{CF} = 3 Hz), 31.7, 36.5 (q, J_{CF} = 2 Hz), 37.7, 46.0 (q, J_{CF} = 27 Hz), 47.4, 127.1 (q, J_{CF} = 277 Hz); ^{19}F NMR: δ_F = 91.8 (d, J_{FH} = 9 Hz); HRMS (FAB): calcd for $C_{11}H_{19}F_3NaS$ ([M+Na]$^+$) 263.1057, found 263.1046.

Diethyl 4-difluoromethylene-2-phenylcyclopentane-1,1-dicarboxylate (24): To a solution of **10** (83 mg, 0.23 mmol) in DMF (3 mL) was added potassium hydride (KH, 30% dispersion in mineral oil; 50 mg, 0.37 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was heated at 110 °C for 3 h. Phosphate buffer (pH 7, 20 mL) was added to quench the reaction, and organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **24** (60 mg, 77%) as a colorless liquid. IR (neat): 3032, 2983, 1772, 1730, 1456, 1367, 1269, 1221, 1036 cm^{-1}; ^{1}H NMR: δ = 0.94 (3H, t, J = 7.1Hz), 1.25 (3H, t, J = 7.1 Hz), 2.71 (1H, dm, J = 16.4 Hz), 2.82 (1H, dm, J = 16.8 Hz), 2.92–2.99 (1H, m), 3.34 (1H, dm, J = 16.8 Hz), 3.71 (1H, dq, J = 10.7, 7.1 Hz), 3.90 (1H, dq, J = 10.7, 7.1 Hz), 4.05 (1H, dd, J = 7.9, 5.8 Hz), 4.18 (1H, dq, J = 10.7, 7.1 Hz), 4.26 (1H, dq, J = 10.7, 7.1 Hz), 7.19–7.28 (5H, m); ^{13}C NMR: δ = 13.5, 13.9, 31.7, 33.2, 49.6, 61.2, 61.7, 65.1, 87.1 (dd, J_{CF} = 23, 22 Hz), 127.3, 128.1, 128.2, 139.8, 150.4 (dd, J_{CF} = 281, 281 Hz), 168.9, 171.0; ^{19}F NMR: δ_F = 71.7 (1F, dm, J_{FF} = 58 Hz), 71.9 (1F, dm, J_{FF} = 58 Hz); elemental analysis: calcd (%) for $C_{18}H_{20}F_2O_4$: C 63.90, H 5.96, found: C 63.74, H 5.89.

4-Difluoromethylene-2-phenylcyclopentane-1,1-dicarbonitrile (25): To a solution of **11** (54 mg, 0.21 mmol) in DMF (3 mL) was added NaH (60% dispersion in mineral oil; 10.6 mg, 0.265 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was heated at 100 °C for 3 h. Phosphate buffer (pH 7, 20 mL) was added to quench the reaction, and organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **25** (31 mg, 61%) as a colorless liquid. IR (neat): 3033, 2935, 2360, 2332, 1772, 1498, 1271, 1078 cm^{-1}; ^{1}H NMR: δ = 2.95 (1H, ddm, J = 15.8, 7.5 Hz), 3.04 (1H, ddm, J = 15.8, 11.3 Hz), 3.16 (1H, dm, J = 15.6 Hz), 3.37 (1H, dm, J = 15.6 Hz), 3.72 (1H, dd, J = 11.3, 7.5 Hz), 7.42–7.48 (5H, m); ^{13}C NMR: δ = 28.4, 38.4 (d, J_{CF} = 3 Hz), 41.5, 54.4, 83.3 (dd, J_{CF} = 27, 23 Hz), 113.4, 114.6, 128.0, 129.2, 129.6, 133.0, 151.5 (dd, J_{CF} = 285, 285 Hz); ^{19}F NMR: δ_F = 76.0 (1F, dm, J_{FF} = 49 Hz), 76.3 (1F, dm, J_{FF} = 49 Hz); elemental analysis: calcd (%) for $C_{14}H_{10}F_2N_2$: C 68.85, H 4.13, N 11.47, found: C 68.83, H 4.21, N 11.37.

Acknowledgements

We are grateful to Central Glass Co., Ltd. for financial support and to Tosoh F-Tech, Inc. for a generous gift of 2-bromo-3,3,3-trifluoroprop-1-ene.

[1] a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun*. **1976**, 734; b) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, R. C. Thomas, *J. Chem. Soc., Chem. Commun*. **1976**, 736; c) J. E. Baldwin, R. C. Thomas, L. Kruse, L. Silberman, *J. Org. Chem*. **1977**, *42*, 3846.

[2] J. Ichikawa, Y. Wada, M. Fujiwara, K. Sakoda, *Synthesis* **2002**, 1917 and references therein.

[3] For recent reports, see: a) J. Ichikawa, G. Lapointe, Y. Iwai, *Chem. Commun*. **2007**, 2698; b) J. J. Caldwell, D. Craig, *Angew. Chem. Int. Ed*. **2007**, *46*, 2631; c) J. J. Caldwell, D. Craig, S. P. East, *ARKIVOC* **2007**, *XII*, 67; d) J. Clayden, D. W. Watson, M. Helliwell, M. Chambers, *Chem. Comm.* **2003**, 2582; e) R. Naitoh, Y. Nakamura, E. Katano, Y. Nakamura, E. Okada, M. Asaoka, *Heterocycles* **2004**, *63*, 1009; f) P. Auvray, P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1985**, *26*, 4455; for recent reports on the cyclization of allenes, see: g) H. Ohno, Y. Kadoh, T. Tanaka, *Org. Lett.* **2006**, *8*, 947; h) M. A. Chowdhury, H.-U. Reissig, *Synlett* **2006**, 2383.

[4] For a recent review, see: a) D. W. Knight in *Progress in Heterocyclic Chemistry* (Ed.: G. W. Gribble, T. L. Gilchrist), Pergamon, Amsterdam, **2002**, Vol. 14, Chap. 2; for recent reports, see: b) A. D. Jones, A. L. Redfern, D. W. Knight, I. R. Morgan, A. C. Williams, *Tetrahedron* **2006**, *62*, 9247; c) N. S. Karanjule, S. D. Markad, V. S. Shinde, D. D. Dhavale, *J. Org. Chem*. **2006**, *71*, 4667.

[5] For recent reports, see: a) A. J. Clark, C. P. Dell, J. M. McDonagh, J. Geden, P. Mawdsley, *Org. Lett.* **2003**, *5*, 2063; b) C. Chatgilialoglu, C. Ferreri, M. Guerra, V. Timokhin, G. Froudakis, T. Gimisis, *J. Am. Chem. Soc.* **2002**, *124*, 10765; for recent reviews, see: c) H. Ishibashi, *Chem. Rec.* **2006**, *6*, 23; d) H. Ishibashi, T. Sato, M. Ikeda, *Synthesis* **2002**, 695; e) A. F. Parsons, *C. R. Acad. Sci.* **2001**, *4*, 391.

[6] a) J. Ichikawa, H. Fukui, Y. Ishibashi, *J. Org. Chem*. **2003**, *68*, 7800 and references therein; b) J.-P. Bégué, D. Bonnet-Delpon, M. H. Rock, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1409 .

[7] a) T. Mori, J. Ichikawa, *Chem. Lett*. **2004**, *33*, 1207; b) T. Mori, Y. Iwai, J. Ichikawa, *Chem. Lett.* **2005**, *34*, 778.

[8] a) *Organofluorine Chemistry: Principles and Commercial Applications* (Ed.: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum Press, New York, **1994**; b) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.

[9] R. Plantier-Royon, C. Portella, *Carbohydr. Res.* **2000**, *327*, 119.

[10] *Biomedical Frontiers of Fluorine Chemistry* (Ed.: I. Ojima, J. R. McCarthy, J. T. Welch), American Chemical Society, Washington, DC, **1996**.

[11] a) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626; b) S. Kaneko, T. Yamazaki, T. Kitazume, *J. Org. Chem*. **1993**, *58*, 2302 and references therein; for a review, see: c) J. T. Welch, *Tetrahedron* **1987**, *43*, 3123.

[12] a) G. Wang, K. Sakthivel, V. Rajappan, T. W. Bruice, K. Tucker, P. Fagan, J. L. Brooks, T. Hurd, J. M. Leeds, P. D. Cook, *Nucleosides, Nucleotides Nucleic Acids* **2004**, *23*, 317; b) S. Marcotte, B. Gerard, X. Pannecoucke, C. Feasson, J.-C. Quirion, *Synthesis* **2001**, 929 and references therein.

[13] V. J. Lee in *Comprehensive Organic Synthesis, Vol. 4* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, p 69.

[14] C. Leriche, X. He, C. T. Chang, H. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 6348 and references therein.

[15] R. Nadano, Y. Iwai, T. Mori, J. Ichikawa, *J. Org. Chem.* **2006**, *71*, 8748 and references therein.

[16] J. Ichikawa, T. Mori, Y. Iwai, *Chem. Lett.* **2004**, *33*, 1354.

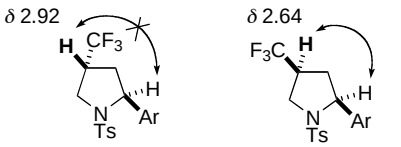
[17] B. Jiang, Q.-F. Wang, C.-G. Tang, M. Xu, *Tetrahedron Lett*. **2001**, *42*, 4083.

[18] T. Yamazaki, N. Ishikawa, *Chem. Lett*. **1984**, 521.

[19] R. Nadano, J. Ichikawa, *Synthesis* **2006**, 128.

[20] O. Mitsunobu, *Synthesis* **1981**, 1.

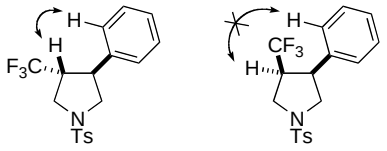
[21] T. Tsunoda, F. Ozaki, S. Ito, *Tetrahedron Lett.* **1994**, *35*, 5081.
[22] For a report on 3-(methylene)indolines, see: J. Barluenga, F. J. Fañanás, R. Sanz, Y. Fernández, *Chem. Eur. J.* **2002**, *8*, 2034.
[23] For recent reports on 3-(trifluoromethyl)indoline derivatives, see: a) N. Shibata, H. Fujimoto, S. Mizuta, S. Ogawa, Y. Ishiuchi, S. Nakamura, T. Toru, *Synlett* **2006**, 3484; b) B. Dolenský, J. Kvíčala, O. Paleta, *J. Fluorine Chem.* **2005**, *126*, 745; c) H. A. Schenck, P. W. Lenkowski, I. Choudhury-Mukherjee, S.-H. Ko, J. P. Stables, M. K. Patel, M. L. Brown, *Bioorg. Med. Chem.* **2004**, *12*, 979; d) V. A. Petrov, *J. Fluorine Chem.* **2000**, *106*, 25.
[24] For recent reports on 3-(trifluoromethyl)indoles, see: a) Y.-Q. Fang, M. Lautens, *Org. Lett.* **2005**, *7*, 3549; b) T. Konno, J. Chae, T. Ishihara, H. Yamanaka, *J. Org. Chem.* **2004**, *69*, 8258 and references therein; c) I. Choudhury-Mukherjee, H. A. Schenck, S. Cechova, N. Pajewski, J. Kapur, J. Ellena, D. S. Cafiso, M. L. Brown, *J. Med. Chem.* **2003**, *46*, 2494; d) I. Rodrigues, D. Bonnet-Delpon, J.-P. Bégué, *J. Org. Chem.* **2001**, *66*, 2098 and references therein.
[25] a) T. Fukuyama, M. Cheung, C.-K. Jow, Y. Hidai, T. Kan, *Tetrahedron Lett.* **1997**, *38*, 5831; b) T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373.
[26] G. Alvernhe, A. Laurent, G. Haufe, *Synthesis* **1987**, 562.
[27] S. Irifune, T. Kibayashi, Y. Ishii, M. Ogawa, *Synthesis* **1988**, 366.
[28] There are no reports on 3-(difluoromethyl)indoles to our knowledge. For recent reports on 2-(difluoromethyl)indoles, see: a) F. Ge, Z. Wang, W. Wan, J. Hao, *Synlett* **2007**, 447; b) ref. 24b.
[29] a) R. D. Chambers, *Fluorine in Organic Chemistry*, Antony Rowe; Chippenham, **1973**, p 1; b) B. E. Smart in *Organofluorine Chemistry: Principles and Commercial Applications* (Ed.: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum Press, New York, **1994**, p 57; c) A. D. Allen, T. T. Tidwell in *Advances in Carbocation Chemistry* (Ed.: X. Creary), Jai Press, Greenwich, **1989**, Vol. 1, p 1.
[30] For recent reports on 3-trifluoromethyl-2,3-dihydrobenzothiophenes, see: a) E. Okada, N. Tsukushi, N. Shimomura, *Synthesis* **2000**, 237; b) M. Yoshimatsu, T. Sugimoto, N. Okada, S. Kinoshita, *J. Org. Chem.* **1999**, *64*, 5162; c) E. Okada, R. Masuda, M. Hojo, N. Imazaki, H. Miya, *Heterocycles* **1992**, *34*, 103.
[31] For recent reports on 3-(difluoromethylene)pyrrolidines, see: a) J. Ichikawa, R. Nadano, N. Ito, *Chem. Commun.* **2006**, 4425; b) X.-L. Qiu, F.-L. Qing, *J. Org. Chem.* **2005**, *70*, 3826; c) A. Kamal, P. S. M. M. Reddy, D. R. Reddy, E. Laxman, Y. L. N. Murthy, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5699; d) X.-L. Qiu, F.-L. Qing, *Synthesis* **2004**, 334; e) X.-L. Qiu, F.-L. Qing, *J. Org. Chem.* **2002**, *67*, 7162.
[32] For recent reports on 3-(trifluoromethyl)pyrrolidines, see: a) T. Llamas, R. G. Arrayás, J. C. Carretero, *Synthesis* **2007**, 950; b) V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, I. V. Martynov, *Russ. Chem. Bull.* **2005**, *54*, 2851; c) C. Brule, J.-P. Bouillon, C. Portella, *Tetrahedron* **2004**, *60*, 9849; d) X.-L. Qiu, F.-L. Qing, *J. Org. Chem.* **2003**, *68*, 3614; e) X.-L. Qiu, F.-L. Qing, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2052; f) J. R. Del Valle, M. Goodman, *Angew. Chem., Int. Ed.* **2002**, *41*, 1600; g) P.-H. Liang, L.-W. Hsin, C.-Y. Cheng, *Bioorg. Med. Chem.* **2002**, *10*, 3267.
[33] The 2,4-*trans/cis* stereochemistry of the pyrrolidine ring was determined by a NOESY experiment on 2-(4-bromophenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (**20b**) as a representative example. A cross peak between the C-2 and C-4 protons was observed in the minor product, but not in the major product. As for the C-4 proton of the pyrrolidine ring, the signal of the *trans*-isomer was observed at lower field (δ 2.92) than that of the *cis*-isomer (δ 2.64), which allowed assignment of the configuration to the other stereoisomers **20a** and **20c**–**d**.



***trans*-20b** (major) ***cis*-20b** (minor)

Ar = C_6H_4-4-Br

[34] The 3,4-*trans/cis* stereochemistry of 1-(4-methylbenzenesulfonyl)-3-phenyl-4-(trifluoromethyl)pyrrolidine (**20e**) was determined by a NOESY experiment. A cross peak between the C-4 proton of the pyrrolidine ring and the *o*-protons of the 3-phenyl group was observed in the major product, but not in the minor product.



***trans*-20e** (major) ***cis*-20e** (minor)

[35] For a recent review on the *gem*-dialkyl effect, see: M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735.
[36] For recent reports on 3-(difluoromethylene)tetrahydrofurans, see: a) A. Gautier, G. Garipova, C. Salcedo, S. Balieu, S. R. Piettre, *Angew. Chem. Int. Ed.* **2004**, *43*, 5963; b) S. Marcotte, B. Gérard, X. Pannecoucke, C. Feasson, J.-C. Quirion, *Synthesis* **2001**, 929. c) P. J. Serafinowski, C. A. Brown, *Tetrahedron* **2000**, *56*, 333; d) ref. 9.
[37] For a recent report on 3-(difluoromethylene)tetrahydrothiophenes, see: M. H. Lim, H. O. Kim, H. R. Moon, M. W. Chun, L. S. Jeong, *Org. Lett.* **2002**, *4*, 529.
[38] For recent reports on 3-(trifluoromethyl)tetrahydrothiophenes, see: a) R. Huisgen, E. Langhals, K. Polborn, K. Karaghiosoff, *Helvetica Chim. Acta* **2004**, *87*, 1426; b) X. Zhang, F.-L. Qing, *J. Org. Chem.* **2002**, *67*, 1016; c) R. Huisgen, X. Li, H. Giera, E. Langhals, *Helvetica Chim. Acta* **2001**, *84*, 981.
[39] For recent reports on (difluoromethylene)cyclopentane derivatives, see: a) H. Yuan, R. B. Silverman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1651; b) Y. Pan, J. Qiu, R. B. Silverman, *J. Med. Chem.* **2003**, *46*, 5292; c) A. Saito, M. Okada, Y. Nakamura, O. Kitagawa, H. Horikawa, T. Taguchi, *J. Fluorine Chem.* **2003**, *123*, 75.
[40] J. R. Henry, L. R. Marcin, M. C. McIntosh, *Tetrahedron Lett.* **1989**, *30*, 5709.
[41] P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85.

Received: ((will be filled in by the editorial staff))
Revised: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))